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Case 5/1254-FL
Priority text

Bicyclic heterocycles, pharmaceutical compositions containing these compounds, their use and processes for preparing them

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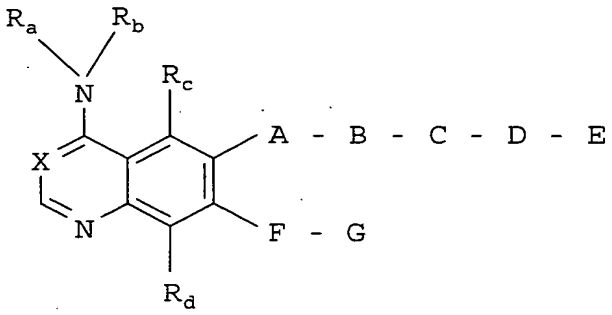
The present invention relates to bicyclic heterocycles of general formula



, (I)

the tautomers, the stereoisomers and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases which have valuable pharmacological properties, particularly an inhibitory effect on signal transduction mediated by tyrosine kinases, their use for treating diseases, particularly tumoral diseases, diseases of the lungs and respiratory tract and the preparation thereof.

In the above general formula I

R_a denotes a hydrogen atom or a C_{1-4}-alkyl group,

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_3, whilst

R_1 and R_2, which may be identical or different, in each case denote a hydrogen, fluorine, chlorine, bromine or iodine atom,

a C_{1-4}-alkyl, hydroxy, C_{1-4}-alkoxy, C_{3-6}-cycloalkyl, C_{4-6}-cycloalkoxy, C_{2-5}-alkenyl or C_{2-5}-alkynyl group,

an aryl, aryloxy, arylmethyl or arylmethoxy group,

a C_{3-5}-alkenyloxy or C_{3-5}-alkynyloxy group, wherein the unsaturated part may not be linked to the oxygen atom,

a C_{1-4}-alkylsulphenyl, C_{1-4}-alkylsulphinyl, C_{1-4}-alkylsulphonyl, C_{1-4}-alkylsulphonyloxy, trifluoromethylsulphenyl, trifluoromethylsulphinyl or trifluoromethylsulphonyl group,

a methyl or methoxy group substituted by 1 to 3 fluorine atoms,

an ethyl or ethoxy group substituted by 1 to 5 fluorine atoms,

a cyano or nitro group or an amino group optionally substituted by one or two C_{1-4}-alkyl groups, while the substituents may be identical or different, or

R_1 together with R_2, if they are bound to adjacent carbon atoms, denote a -CH=CH-CH=CH, -CH=CH-NH or -CH=N-NH -group and

R_3 denotes a hydrogen, fluorine, chlorine or bromine atom,

a C_{1-4}-alkyl, trifluoromethyl or C_{1-4}-alkoxy group,

R_c and R_d, which may be identical or different, in each case denote a hydrogen, fluorine or chlorine atom, a methoxy group

or a methyl group optionally substituted by a methoxy, dimethylamino, diethylamino, pyrrolidino, piperidino or morpholino group,

X denotes a methine group substituted by a cyano group or a nitrogen atom,

A denotes an oxygen atom or an imino group optionally substituted by a C_{1-4}-alkyl group,

B denotes a carbonyl or sulphonyl group,

C denotes a 1,3-allenylene, 1,1- or 1,2-vinylene group which may be substituted in each case by one or two methyl groups or by a trifluoromethyl group,

an ethynylene group or

a 1,3-butadien-1,4-ylene group optionally substituted by 1 to 4 methyl groups or by a trifluoromethyl group,

D denotes an alkylene, -CO-alkylene or -SO_2-alkylene group wherein the alkylene moiety in each case contains 1 to 8 carbon atoms and additionally 1 to 4 hydrogen atoms in the alkylene moiety may be replaced by fluorine atoms, while the linking of the -CO-alkylene or -SO_2-alkylene group to the adjacent group C in each case must take place via the carbonyl or sulphonyl group,

a -CO-O-alkylene, -CO-NR_4-alkylene or -SO_2-NR_4-alkylene group wherein the alkylene moiety in each case contains 1 to 8 carbon atoms, while the linking to the adjacent group C in each case must take place via the carbonyl or sulphonyl group wherein

R_4 denotes a hydrogen atom or a C_{1-4}-alkyl group,

or, if D is bound to a carbon atom of the group E, it may also denote a bond

or, if D is bound to a nitrogen atom of the group E, it may also denote a carbonyl or sulphonyl group,

E denotes an R_6O-CO-alkylene-NR_5, (R_7O-PO-OR_8)-alkylene-NR_5 or (R_7O-PO-R_9)-alkylene-NR_5 group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C_{1-2}-alkyl groups or by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group, wherein

R_5 denotes a hydrogen atom,

a C_{1-4}-alkyl group, which may be substituted by a hydroxy, C_{1-4}-alkoxy, carboxy, R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), amino, C_{1-4}-alkylamino or di-(C_{1-4}-alkyl)-amino group or by a 4- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, or by a sulphinyl, sulphonyl, imino or N-(C_{1-4}-alkyl)-imino group,

a C_{3-7}-cycloalkyl or C_{3-7}-cycloalkyl-C_{1-3}-alkyl group,

R_6, R_7 and R_8, which may be identical or different, in each case denote a hydrogen atom,

a C_{1-8}-alkyl group, which may be substituted by a hydroxy, C_{1-4}-alkoxy, amino, C_{1-4}-alkylamino or di-(C_{1-4}-alkyl)-amino group or by a 4- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-4}-alkyl)-imino group,

a C_{4-7}-cycloalkyl group optionally substituted by 1 or 2 methyl groups,

a C_{3-5}-alkenyl or C_{3-5}-alkynyl group, while the unsaturated part may not be linked to the oxygen atom,

a C_{3-7}-cycloalkyl-C_{1-4}-alkyl, aryl, aryl-C_{1-4}-alkyl or R_gCO-O-(R_eCR_f)-group, whilst

R_e and R_f, which may be identical or different, in each case denote a hydrogen atom or a C_{1-4}-alkyl group and

R_g denotes a C_{1-4}-alkyl, C_{3-7}-cycloalkyl, C_{1-4}-alkoxy or C_{5-7}-cycloalkoxy group,

and R_9 denotes a C_{1-4}-alkyl, aryl or aryl-C_{1-4}-alkyl group,

a 4- to 7-membered alkyleneimino group which may be substituted by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and is additionally substituted at a cyclic carbon atom by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-pO-OR_8)-C_{1-4}-alkyl or (R_7O-pO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined and

R_{10} denotes a hydrogen atom, a C_{1-4}-alkyl, formyl, C_{1-4}-alkylcarbonyl or C_{1-4}-alkylsulphonyl group,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10}, while the abovementioned 5- to 7-membered rings are additionally substituted in each case at a carbon atom by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_{10} are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group, wherein R_6 to R_9 are as hereinbefore defined,

a 2-oxo-morpholino group which may be substituted by 1 or 2 methyl groups,

an amino group or an amino group optionally substituted by 1 or 2 C_{1-4}-alkyl groups wherein the alkyl groups may be identical or different and each alkyl moiety may be substituted from position 2 by a hydroxy, C_{1-4}-alkoxy, amino, C_{1-4}-alkylamino or di-(C_{1-4}-alkyl)-amino group or by a 4- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group may be replaced in the 4 position by an oxygen or sulphur atom, or by a sulphinyl, sulphonyl, imino or N-(C_{1-4}-alkyl)-imino group,

an 4- to 7-membered alkyleneimino group optionally substituted by 1 to 4 methyl groups,

a 6- to 7-membered alkyleneimino group optionally substituted by 1 or 2 methyl groups wherein in each case a methylene group in the 4 position is replaced by an oxygen or sulphur atom, by an imino group substituted by the group R_{10}, by a sulphinyl or sulphonyl group, whilst R_{10} is as hereinbefore defined,

an imidazolyl group optionally substituted by 1 to 3 methyl groups,

a C_{5-7}-cycloalkyl group wherein a methylene group is replaced by an oxygen or sulphur atom, by an imino group substituted by the group R_{10}, by a sulphinyl or sulphonyl group, wherein R_{10} is as hereinbefore defined,

or D together with E denotes a hydrogen, fluorine or chlorine atom,

a C_{1-4}-alkyl group optionally substituted by 1 to 5 fluorine atoms,

a C_{3-6}-cycloalkyl group,

an aryl, heteroaryl, C_{1-4}-alkylcarbonyl, arylcarbonyl, carboxy, C_{1-4}-alkoxycarbonyl, $R_9CO-O-(R_eCR_f)-O-CO$, $(R_7O-PO-OR_8)$ or $(R_7O-PO-R_9)$-group wherein R_e to R_g and R_7 to R_9 are as hereinbefore defined,

an aminocarbonyl, C_{1-4}-alkylaminocarbonyl or di-$(C_{1-4}$-alkyl)-aminocarbonyl group or

a carbonyl group, which is substituted by a 4- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups a methylene group in the 4 position may be replaced in each case by an oxygen or sulphur atom, by an imino group substituted by the group R_{10}, by a sulphinyl or sulphonyl group, wherein R_{10} is as hereinbefore defined,

F denotes a C_{1-6}-alkylene group, an $-O-C_{1-6}$-alkylene group, whilst the alkylene moiety is linked to the group G, or an oxygen atom, whilst the latter may not be linked to a nitrogen atom of the group G, and

G denotes an R_6O-CO-alkylene-NR_5, (R_7O-PO-OR_8)-alkylene-NR_5 or (R_7O-PO-R_9)-alkylene-NR_5-group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C_{1-2}-alkyl groups or by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group, wherein R_5 to R_9 are as hereinbefore defined,

a 4- to 7-membered alkyleneimino group which is substituted by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and is additionally substituted at a cyclic carbon atom by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_{10} are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10}, whilst the above mentioned 5- to 7-membered rings are additionally substituted in each case at a carbon atom by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_{10} are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group, wherein R_6 to R_9 are as hereinbefore defined,

a 2-oxo-morpholino group which may be substituted by 1 or 2 methyl groups,

a 2-oxo-morpholinyl group which is substituted in the 4 position by a hydrogen atom, by a C_{1-4}-alkyl, R_6O-CO-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group, while R_6 to R_9 are as hereinbefore defined and the abovementioned 2-oxo-morpholinyl groups are linked in each case to a carbon atom of the group F,

an amino group or an amino group optionally substituted by 1 or 2 C_{1-4}-alkyl groups wherein the alkyl groups may be identical or different and each alkyl moiety may be substituted from position 2 by a hydroxy, C_{1-4}-alkoxy, amino, C_{1-4}-alkylamino or di-(C_{1-4}-alkyl)-amino group or by a 4- to 7-membered alkyleneimino group, wherein in the above mentioned 6- to 7-membered alkyleneimino groups a methylene group in the 4 position may be replaced in each case by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-4}-alkyl)-imino group,

a 4- to 7-membered alkyleneimino group optionally substituted by 1 to 4 methyl groups,

a 6- to 7-membered alkyleneimino group optionally substituted by 1 or 2 methyl groups wherein in each case a methylene group in the 4 position is replaced by an oxygen or sulphur atom, by an imino group substituted by the group R_{10}, or by a sulphinyl or sulphonyl group, wherein R_{10} is as hereinbefore defined,

an imidazolyl group optionally substituted by 1 to 3 methyl groups,

a C_{5-7}-cycloalkyl group wherein a methylene group is replaced by an oxygen or sulphur atom, by an imino group substituted by the group R_{10}, or by a sulphinyl or sulphonyl group, wherein R_{10} is as hereinbefore defined, or

F and G together denote a hydrogen, fluorine or chlorine atom,

a C_{1-6}-alkoxy group optionally substituted from position 2 by a hydroxy or C_{1-4}-alkoxy group,

a C_{1-6}-alkoxy group which is substituted by an R_6O-CO, (R_7O-PO-OR_8) or (R_7O-PO-R_9)-group, while R_6 to R_9 are as hereinbefore defined,

a C_{4-7}-cycloalkoxy or C_{3-7}-cycloalkyl-C_{1-4}-alkoxy group, an amino group optionally substituted by 1 or 2 C_{1-4}-alkyl groups,

a 5- to 7-membered alkyleneimino group, wherein in the abovementioned 6- to 7-membered alkyleneimino groups a methylene group in the 4 position may be replaced in each case by an oxygen or sulphur atom, by an imino group substituted by the group R_{10}, or by a sulphinyl or sulphonyl group, wherein R_{10} is as hereinbefore defined,

with the proviso that at least one of the groups E, G or F together with G denotes a R_6O-CO, (R_7O-PO-OR_8) or (R_7O-PO-R_9)-group or

D together with E contains an R_gCO-O-(R_eCR_f)-O-CO, (R_7O-pO-OR_8) or (R_7O-pO-R_9)-group or

E or G contains an optionally substituted 2-oxo-morpholinyl group.

By the aryl moieties mentioned in the definitions of the abovementioned groups is meant a phenyl group which in each case may be monosubstituted by R_{12}, mono-, di- or trisubstituted by R_{13} or monosubstituted by R_{12} and additionally mono- or disubstituted by R_{13}, whilst the substituents may be identical or different and

R_{12} denotes a cyano, carboxy, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-4}-alkylaminocarbonyl, di-(C_{1-4}-alkyl)-aminocarbonyl, C_{1-4}-alkylsulphenyl, C_{1-4}-alkylsulphinyl, C_{1-4}-alkylsulphonyl, hydroxy, C_{1-4}-alkylsulphonyloxy, trifluoromethyloxy, nitro, amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, C_{1-4}-alkylcarbonylamino, N-(C_{1-4}-alkyl)-C_{1-4}-alkylcarbonylamino, C_{1-4}-alkylsulphonylamino, N-(C_{1-4}-alkyl)-C_{1-4}-alkylsulphonylamino, aminosulphonyl, C_{1-4}-alkylaminosulphonyl or di-(C_{1-4}-alkyl)-aminosulphonyl group or a carbonyl group, which is substituted by a 5- to 7-membered alkyleneimino group, wherein in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-4}-alkyl)-imino group, and

R_{13} denotes a fluorine, chlorine, bromine or iodine atom, a C_{1-4}-alkyl, trifluoromethyl or C_{1-4}-alkoxy group or

two groups R_{13}, if they are bound to adjacent carbon atoms, together denote a C_{3-5}-alkylene, methylenedioxy or 1,3-butadien-1,4-ylene group.

Moreover, the heteroaryl groups mentioned in the definitions of the abovementioned groups also include a 5-membered heteroaromatic group which contains an imino group, an oxygen or sulphur atom or an imino group, an oxygen or sulphur atom and one or two nitrogen atoms, or

a 6-membered heteroaromatic group, which contains one, two or three nitrogen atoms,

whilst the abovementioned 5-membered heteroaromatic groups may be substituted in each case by 1 or 2 methyl or ethyl groups and the abovementioned 6-membered heteroaromatic groups may be substituted in each case by 1 or 2 methyl or ethyl groups or by a fluorine, chlorine, bromine or iodine atom, or by a trifluoromethyl, hydroxy, methoxy or ethoxy group.

Preferred compounds of the above general formula I are those wherein

R_a denotes a hydrogen atom,

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_3, wherein

R_1 and R_2, which may be identical or different, in each case denote a hydrogen, fluorine, chlorine or bromine atom,

a methyl, trifluoromethyl, ethynyl, methoxy or cyano group and

R_3 denotes a hydrogen atom,

R_c and R_d in each case denote a hydrogen atom,

X denotes a methine group substituted by a cyano group or a nitrogen atom,

A denotes an imino group,

B denotes a carbonyl group,

C denotes a 1,1- or 1,2-vinylene group, an ethynylene or 1,3-butadien-1,4-ylene group,

D denotes a straight-chained C_{1-3}-alkylene group or a -CO-NH-C_{2-3}-alkylene group wherein the alkylene moiety is a straight chain and the linking to the adjacent group C takes place via the carbonyl group,

or, if D is bound to a carbon atom of the group E, it may also denote a bond,

E denotes an R_6O-CO-alkylene-NR_5-group wherein the alkylene moiety, which is straight-chained and contains 1 to 3 carbon atoms, may additionally be substituted by a methyl, methoxycarbonyl, ethoxycarbonyl, methoxycarbonylmethyl or ethoxycarbonylmethyl group, wherein

R_5 denotes a C_{1-4}-alkyl, R_6O-CO-CH_2, cyclopropyl or cyclopropylmethyl group and

R_6 denotes a C_{1-6}-alkyl, cyclopentyl, cyclohexyl, C_{3-6}-cycloalkylmethyl or benzyl group,

a pyrrolidino or piperidino group substituted by an R_6O-CO-group or a piperidino group substituted by an R_6O-CO-CH_2-group wherein R_6 is as hereinbefore defined,

a 4-piperidinyl group, which is substituted in the 1 position by an R_6O-CO-C_{1-3}-alkyl group wherein the alkyl moiety is straight-chained and R_6 is as hereinbefore defined,

a piperazino group which is substituted in the 4 position by an R_6O-CO-C_{1-3}-alkyl group wherein the alkyl moiety is straight-chained and R_6 is as hereinbefore defined,

a piperazino group which is substituted in the 4 position by a methyl group and in the 2 or 3 position by an R_6O-CO- group, wherein R_6 is as hereinbefore defined,

an (R_7O-PO-OR_8)-CH_2-NR_5 or (R_7O-PO-R_9)-CH_2-NR_5-group, wherein R_5 is as hereinbefore defined,

R_7 and R_8, which may be identical or different, in each case denote a methyl, ethyl or R_gCO-O-(R_eCR_f) group, wherein

R_e denotes a hydrogen atom or a C_{1-4}-alkyl group,

R_f denotes a hydrogen atom and

R_g denotes a C_{1-4}-alkyl, C_{1-4}-alkoxy or C_{5-6}-cycloalkoxy group,

and R_9 denotes a methyl or ethyl group,

or D together with E denotes a hydrogen atom, a methyl, trifluoromethyl, phenyl or $R_gCO-O-(R_eCR_f)-O-CO$ group wherein R_e to R_g are as hereinbefore defined,

F denotes an $-O-C_{1-4}$-alkylene group wherein the alkylene moiety, which is preferably straight-chained, is linked to the group G, or an oxygen atom, although this may not be linked to a nitrogen atom of the group G, and

G denotes an R_6O-CO-alkylene-NR_5-group wherein the alkylene moiety, which is straight-chained and contains 1 to 3 carbon atoms, may additionally be substituted by a methyl, methoxycarbonyl, ethoxycarbonyl, methoxycarbonylmethyl or ethoxycarbonylmethyl group, while R_5 and R_6 are as hereinbefore defined,

a pyrrolidino or piperidino group substituted by an R_6O-CO-group or a piperidino group substituted by an $R_6O-CO-CH_2$-group wherein R_6 is as hereinbefore defined,

a 4-piperidinyl group, which is substituted in the 1 position by an $R_6O-CO-C_{1-3}$-alkyl group, wherein the alkyl moiety is straight-chained and R_6 is as hereinbefore defined,

a piperazino group which is substituted in the 4 position by an $R_6O-CO-C_{1-3}$-alkyl group, wherein the alkyl moiety is straight-chained and R_6 is as hereinbefore defined,

or F and G together denote a hydrogen atom or a C_{1-3}-alkoxy group optionally substituted by an R_6O-CO-group wherein R_6 is as hereinbefore defined,

with the proviso that at least one of the groups E, G or F together with G contains an R_6O-CO, (R_7O-PO-OR_8) or (R_7O-PO-CH_3)-group or

D together with E contains an R_gCO-O-(R_eCR_f)-O-CO-group,

the tautomers, the stereoisomers and the salts thereof.

Particularly preferred compounds of the above general formula I are those wherein

R_a denotes a hydrogen atom,

R_b denotes a phenyl group substituted by the groups R_1 to R_3 wherein

R_1 and R_2, which may be identical or different, in each case denote a hydrogen, fluorine, chlorine or bromine atom and

R_3 denotes a hydrogen atom,

R_c and R_d in each case denote a hydrogen atom,

X denotes a nitrogen atom,

A denotes an imino group,

B denotes a carbonyl group,

C denotes a 1,2-vinylene group,

D denotes a methylene or -CO-NH-C_{2-3}-alkylene group wherein the alkylene moiety is a straight chain and the linking to the adjacent group C takes place via the carbonyl group,

E denotes an R_6O-CO-CH_2-NR_5 group wherein

R_5 denotes a methyl or R_6O-CO-CH_2 group and R_6 in each case denotes a C_{1-4}-alkyl or cyclohexyl group,

or D together with E denotes a hydrogen atom or a methyl group,

F denotes a -O-C_{1-3}-alkylene group wherein the alkylene moiety is straight-chained and is linked to the group G, or an oxygen atom, although this may not be linked to a nitrogen atom of the group G, and

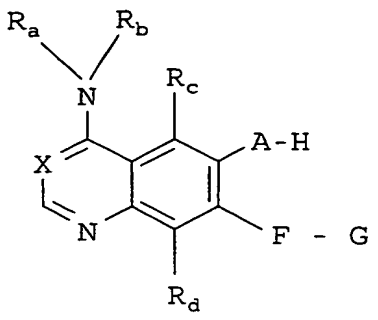
G denotes a 4-piperidinyl group which is substituted in the 1 position by an R_6O-CO-C_{1-3}-alkyl group, or a piperazino group which is substituted in the 4 position by an R_6O-CO-C_{1-3}-alkyl group wherein in each case the alkyl moiety is straight-chained and R_6 is as hereinbefore defined,

or F and G together denote a hydrogen atom or a methoxy group with the proviso that at least one of the groups E or G contains an R_6O-CO-group,

the tautomers, the stereoisomers and the salts thereof.

The compounds of general formula I may be prepared, for example, by the following processes:

a) reacting a compound of general formula



, (II)

wherein
R_a to R_d, A, F, G and X are as hereinbefore defined, with a compound of general formula

$$Z_1 - B - C - D - E \qquad , (III)$$

wherein
B to E are as hereinbefore defined and
Z_1 denotes a leaving group such as a halogen atom, e.g. a chlorine or bromine atom, or a hydroxy group.

The reaction is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane optionally in the presence of an inorganic or organic base and optionally in the presence of a dehydrating agent expediently at temperatures between -50 and 150°C, preferably at temperatures between -20 and 80°C.

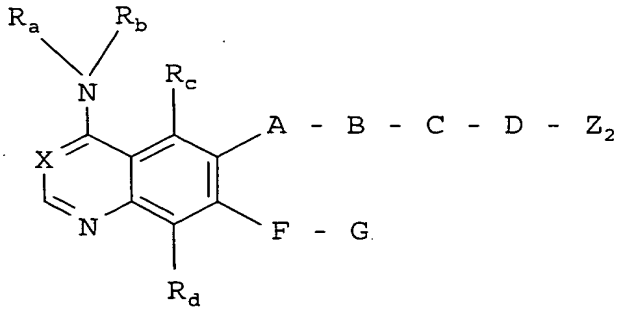
With a compound of general formula III, wherein Z_1 denotes a leaving group, the reaction is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, conveniently in the presence of a tertiary organic base such as triethylamine, pyridine or 2-dimethylaminopyridine, in the presence of N-ethyl-diisopropylamine (Hünig's base), while these organic bases may simultaneously serve as solvent, or in the presence of an inorganic base such as sodium carbonate,

potassium carbonate or sodium hydroxide solution expediently at temperatures between -50 and 150°C, preferably at temperatures between -20 and 80°C.

With a compound of general formula III, wherein Z_1 denotes a hydroxy group, the reaction is preferably carried out in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethyl chlorosilane, phosphorus trichloride, phosphorus pentoxide, hexamethyldisilazane, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxy-benzotriazole and optionally also in the presence of 4-dimethylamino-pyridine, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride conveniently in a solvent such as methylene chloride, tetrahydrofuran, dioxane, toluene, chlorobenzene, dimethylsulphoxide, ethyleneglycol monomethylether, ethyleneglycol diethylether or sulpholane and optionally in the presence of a reaction accelerator such as 4-dimethylaminopyridine at temperatures between -50 and 150°C, but preferably at temperatures between -20 and 80°C.

b) In order to prepare compounds of general formula I, wherein the group E is linked to the group D via a nitrogen atom:

reacting a compound of general formula



, (IV)

wherein
R_a to R_d, A to D, F, G and X are as hereinbefore defined and Z_2 denotes a leaving group such as a halogen atom, a substituted hydroxy or sulphonyloxy group such as a chlorine or bromine atom, a methanesulphonyloxy or p-toluenesulphonyloxy group, with a compound of general formula

$$H - E' \quad , \quad (V)$$

wherein
E´ denotes one of the groups mentioned for E hereinbefore, which is linked to the group D via a nitrogen atom.

The reaction is conveniently carried out in a solvent such as isopropanol, butanol, tetrahydrofuran, dioxan, toluene, chlorobenzene, dimethylformamide, dimethylsulphoxide, methylene chloride, ethyleneglycol monomethylether, ethyleneglycol diethylether or sulpholane, optionally in the presence of an inorganic or tertiary organic base, e.g. sodium carbonate or potassium hydroxide, a tertiary organic base, e.g. triethylamine, or in the presence of N-ethyl-diisopropylamine (Hünig's base), whilst these organic bases may simultaneously serve as solvent, and optionally in the presence of a reaction accelerator such as an alkali metal halide at temperatures between -20 and 150°C, but preferably at temperatures between -10 and 100°C. The reaction may, however, also be carried out without a solvent or in an excess of the compound of general formula V used.

If according to the invention a compound of general formula I is obtained which contains an amino, alkylamino or imino group, this may be converted by acylation or sulphonylation into a corresponding acyl or sulphonyl compound of general formula I or

if a compound of general formula I is obtained which contains an amino, alkylamino or imino group, this may be converted by alkylation or reductive alkylation into a corresponding alkyl compound of general formula I or

if a compound of general formula I is obtained which contains a carboxy or hydroxyphosphoryl group, this may be converted by esterification into a corresponding ester of general formula I or

if a compound of general formula I is obtained which contains a carboxy or ester group, this can be converted by reaction with an amine into a corresponding amide of general formula I.

The subsequent esterification is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamidee, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane or particularly advantageously in a corresponding alcohol, optionally in the presence of an acid such as hydrochloric acid or in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethyl chlorosilane, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxy-benzotriazole and optionally additionally in the presence of 4-dimethylamino-pyridine, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

The subsequent ester formation may also be carried out by reacting a compound which contains a carboxy or hydroxyphosphoryl group with a corresponding alkyl halide.

The subsequent acylation or sulphonylation is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane with a corresponding acyl or sulphonyl derivative optionally in the presence of a tertiary organic base or in the presence of an inorganic base or in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethyl chlorosilane, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxy-benzotriazole and optionally additionally in the presence of 4-dimethylamino-pyridine, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, expediently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

The subsequent alkylation is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane with an alkylating agent such as a corresponding halide or sulphonic acid ester, e.g. with methyl iodide, ethyl bromide, dimethylsulphate or benzyl chloride, optionally in the presence of a tertiary organic base or in the presence of an inorganic base, expediently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C.

The subsequent reductive alkylation is carried out with a corresponding carbonyl compound such as formaldehyde, acetaldehyde, propionaldehyde, acetone or butyraldehyde in the presence of a complex metal hydride such as sodium borohydride, lithium borohydride, sodium triacetoxyborohydride or sodium cyanoborohydride expediently at a pH of 6-7 and at ambient temperature or in the presence of a hydrogenation

catalyst, e.g. with hydrogen in the presence of palladium/charcoal, at a hydrogen pressure of 1 to 5 bar. The methylation may also be carried out in the presence of formic acid as reducing agent at elevated temperatures, e.g. at temperatures between 60 and 120°C.

The subsequent amide formation is carried out by reacting a corresponding reactive carboxylic acid derivative with a corresponding amine optionally in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, whilst the amine used may simultaneously serve as solvent, optionally in the presence of a tertiary organic base or in the presence of an inorganic base or with a corresponding carboxylic acid in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethyl chlorosilane, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxy-benzotriazole and optionally additionally in the presence of 4-dimethylamino-pyridine, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, expediently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

In the reactions described above, any reactive groups present such as hydroxy, carboxy, phosphono, O-alkyl-phosphono, amino, alkylamino or imino groups may be protected during the reaction by conventional protecting groups which are cleaved again after the reaction.

For example, a protecting group for a hydroxy group may be a trimethylsilyl, acetyl, benzoyl, methyl, ethyl, tert. butyl, trityl, benzyl or tetrahydropyranyl group,

protecting groups for a carboxy group may be the trimethylsilyl, methyl, ethyl, tert. butyl, benzyl or tetrahydropyranyl group,

protecting groups for a phosphono group may be an alkyl group such as the methyl, ethyl, isopropyl or n-butyl group, the phenyl or benzyl group and

protecting groups for an amino, alkylamino or imino group may be a formyl, acetyl, trifluoroacetyl, ethoxycarbonyl, tert.-butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group and for the amino group additionally a phthalyl group.

Any protecting group used is optionally subsequently cleaved for example by hydrolysis in an aqueous solvent, e.g. in water, isopropanol/water, acetic acid/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as sodium hydroxide or potassium hydroxide or aprotically, e.g. in the presence of iodotrimethylsilane, at temperatures between 0 and 120°C, preferably at temperatures between 10 and 100°C.

However, a benzyl, methoxybenzyl or benzyloxycarbonyl group is cleaved, for example, hydrogenolytically, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid at temperatures between 0 and 100°C, but preferably at temperatures between 20 and 60°C, and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar. A 2,4-dimethoxybenzyl group, however, is preferably cleaved in trifluoroacetic acid in the presence of anisol.

A tert-butyl or tert.butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid

or hydrochloric acid or by treating with iodotrimethylsilane optionally using a solvent such as methylene chloride, dioxane, methanol or diethylether.

A trifluoroacetyl group is preferably cleaved by treating with an acid such as hydrochloric acid, optionally in the presence of a solvent such as acetic acid at temperatures between 50 and 120°C or by treating with sodium hydroxide solution optionally in the presence of a solvent such as tetrahydrofuran at temperatures between 0 and 50°C.

A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxane at temperatures between 20 and 50°C.

A single alkyl group may be cleaved from an O,O'-dialkylphosphono group with sodium iodide, for example, in a solvent such as acetone, methylethylketone, acetonitrile or dimethylformamide at temperatures between 40 and 150°C, but preferably at temperatures between 60 and 100°C.

Both alkyl groups may be cleaved from an O,O'-dialkyl-phosphono group with iodotrimethylsilane, bromotrimethylsilane or chlorotrimethylsilane/sodium iodide, for example, in a solvent such as methyl chloride, chloroform or acetonitrile at temperatures between 0°C and the boiling temperature of the reaction mixture, but preferably at temperatures between 20 and 60°C.

Moreover, the compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers, as mentioned hereinbefore. Thus, for example, cis/trans mixtures may be resolved into their cis and trans isomers, and compounds with at least one optically active carbon atom may be separated into their enantiomers.

Thus, for example, the cis/trans mixtures may be resolved by chromatography into the cis and trans isomers thereof, the compounds of general formula I obtained which occur as racemates may be separated by methods known *per se* (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known *per se*, e.g. by chromatography and/or fractional crystallisation, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as e.g. esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e.g. on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active acids in common use are e.g. the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid or quinic acid. An optically active alcohol may be for example (+) or (-)-menthol and an optically active acyl group in amides, for example, may be a (+)-or (-)-menthyloxycarbonyl.

Furthermore, the compounds of formula I may be converted into the salts thereof, and particularly for pharmaceutical use into the physiologically acceptable salts with inorganic or organic acids. Acids which may be used for this purpose include for

example hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

Moreover, if the new compounds of formula I thus obtained contain a carboxy, hydroxyphosphoryl, sulpho or 5-tetrazolyl group, they may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, particularly for pharmaceutical use into the physiologically acceptable salts thereof. Suitable bases for this purpose include for example sodium hydroxide, potassium hydroxide, arginine, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

The compounds of general formulae II to V used as starting materials are known from the literature in some cases or may be obtained by methods known from the literature (cf. Examples I to VII).

For example, a starting compound of general formula II is obtained by reacting a fluoronitro compound correspondingly substituted in the 6 position with a corresponding alkoxide and subsequently reducing the nitro compound thus obtained or

a starting compound of general formula IV is obtained by reacting a fluoronitro compound correspondingly substituted in the 6 position with a corresponding alkoxide, subsequently reducing the nitro compound thus obtained and then acylating with a corresponding compound.

As already mentioned hereinbefore, the compounds of general formula I according to the invention and the physiologically acceptable salts thereof have valuable pharmacological properties, particularly an inhibiting effect on signal transduction mediated by the Epidermal Growth Factor receptor (EGF-R), whilst this may be achieved for example by inhibiting ligand bonding, receptor dimerisation or tyrosinekinase

itself. It is also possible to block the transmission of signals to components located further down.

The biological properties of the new compounds were investigated as follows:

The inhibition of the EGF-R-mediated signal transmission can be demonstrated e.g. with cells which express human EGF-R and whose survival and proliferation depend on stimulation by EGF or TGF-alpha. A cell line of murine origin dependent on interleukin-3(IL-3) which was genetically modified to express functional human EGF-R was used here. The proliferation of these cells known as F/L-HERc can therefore be stimulated either by murine IL-3 or by EGF (cf. von Rüden, T. et al. in EMBO J. 7, 2749-2756 (1988) and Pierce, J. H. et al. in Science 239, 628-631 (1988)).

The starting material used for the F/L-HERc cells was the cell line FDC-P_1, the production of which has been described by Dexter, T. M. et al. in J. Exp. Med. 152, 1036-1047 (1980). Alternatively, however, other growth-factor-dependent cells may also be used (cf. for example Pierce, J. H. et al. in Science 239, 628-631 (1988), Shibuya, H. et al. in Cell 70, 57-67 (1992) and Alexander, W. S. et al. in EMBO J. 10, 3683-3691 (1991)). For expressing the human EGF-R cDNA (cf. Ullrich, A. et al. in Nature 309, 418-425 (1984)) recombinant retroviruses were used as described by von Rüden, T. et al., EMBO J. 7, 2749-2756 (1988), except that the retroviral vector LXSN (cf. Miller, A. D. et al. in BioTechniques 7, 980-990 (1989)) was used for the expression of the EGF-R cDNA and the line GP+E86 (cf. Markowitz, D. et al. in J. Virol. 62, 1120-1124 (1988)) was used as the packaging cell.

The test was performed as follows:

F/L-HERc cells were cultivated in RPMI/1640 medium (BioWhittaker), supplemented with 10 % foetal calf serum (FCS,

Boehringer Mannheim), 2 mM glutamine (BioWhittaker), standard antibiotics and 20 ng/ml of human EGF (Promega), at 37°C and 5% CO_2. In order to investigate the inhibitory activity of the compounds according to the invention, 1.5×10^4 cells per well were cultivated in triplicate in 96-well plates in the above medium (200 µl), the cell proliferation being stimulated with either EGF (20 ng/ml) or murine IL-3. The IL-3 used was obtained from culture supernatants of the cell line X63/0 mIL-3 (cf. Karasuyama, H. et al.in Eur. J. Immunol. 18, 97-104 (1988)). The compounds according to the invention were dissolved in 100% dimethylsulphoxide (DMSO) and added to the cultures in various dilutions, the maximum DMSO concentration being 1%. The cultures were incubated for 48 hours at 37°C.

In order to determine the inhibitory activity of the compounds according to the invention the relative cell number was measured in O.D. units using the Cell Titer 96™ AQueous Non-Radioactive Cell Proliferation Assay (Promega). The relative cell number was calculated as a percentage of the control (F/LHERc cells without inhibitor) and the concentration of active substance which inhibits the proliferation of the cells by 50% (IC_{50}) was derived therefrom. The following results were obtained:

Compound (Example no.)	Inhibition of EGF-dependent proliferation IC_{50} [nM]
1	2.6

The compounds of general formula I according to the invention thus inhibit the signal transduction by tyrosine kinases, as demonstrated by the example of the human EGF receptor, and are therefore useful for treating pathophysiological processes caused by hyperfunction of tyrosine kinases. These are e.g. benign or malignant tumours, particularly tumours of epithelial and neuroepithelial origin, metastasisation and the

abnormal proliferation of vascular endothelial cells (neoangiogenesis).

The compounds according to the invention are also useful for preventing and treating diseases of the airways and lungs which are accompanied by increased or altered production of mucus caused by stimulation by tyrosine kinases, e.g. in inflammatory diseases of the airways such as chronic bronchitis, chronic obstructive bronchitis, asthma, bronchiectasias, allergic or non-allergic rhinitis or sinusitis, cystic fibrosis, α1-antitrypsin deficiency, or coughs, pulmonary emphysema, pulmonary fibrosis and hyperreactive airways.

The compounds are also suitable for treating diseases of the gastrointestinal tract and bile duct and gall bladder which are associated with disrupted activity of the tyrosine kinases, such as may be found e.g. in chronic inflammatory changes such as cholecystitis, Crohn's disease, ulcerative colitis, and ulcers in the gastrointestinal tract or such as may occur in diseases of the gastrointestinal tract which are associated with increased secretions, such as Ménétrier's disease, secreting adenomas and protein loss syndrome.

In addition, the compounds of general formula I and the physiologically acceptable salts thereof may be used to treat other diseases caused by abnormal function of tyrosine kinases, such as e.g. epidermal hyperproliferation (psoriasis), inflammatory processes, diseases of the immune system, hyperproliferation of haematopoietic cells, etc.

By reason of their biological properties the compounds according to the invention may be used on their own or in conjunction with other pharmacologically active compounds, for example in tumour therapy, in monotherapy or in conjunction with other anti-tumour therapeutic agents, for example in combination with topoisomerase inhibitors (e.g. etoposide),

mitosis inhibitors (e.g. vinblastin), compounds which interact with nucleic acids (e.g. cis-platin, cyclophosphamide, adriamycin), hormone antagonists (e.g. tamoxifen), inhibitors of metabolic processes (e.g. 5-FU etc.), cytokines (e.g. interferons), antibodies, etc. For treating respiratory tract diseases, these compounds may be used on their own or in conjunction with other therapeutic agents for the airways, such as substances with a secretolytic, broncholytic and/or antiinflammatory activity. For treating diseases in the region of the gastrointestinal tract, these compounds may also be administered on their own or in conjunction with substances having an effect on motility or secretion. These combinations may be administered either simultaneously or sequentially.

These compounds may be administered either on their own or in conjunction with other active substances by intravenous, subcutaneous, intramuscular, intraperitoneal or intranasal route, by inhalation or transdermally or orally, whilst aerosol formulations are particularly suitable for inhalation.

For pharmaceutical use the compounds according to the invention are generally used for warm-blooded vertebrates, particularly humans, in doses of 0.01-100 mg/kg of body weight, preferably 0.1-15 mg/kg. For administration they are formulated with one or more conventional inert carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethyleneglycol, propyleneglycol, stearylalcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof in conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions, solutions, sprays or suppositories.

The following Examples are intended to illustrate the present invention without restricting it:

Preparation of the starting compounds:

Example I

6-Amino-4-[(3-bromophenyl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-quinazoline

180 mg of iron powder are added to 465 mg of 4-[(3-bromophenyl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-nitro-quinazoline in 20 ml of ethanol. The reaction mixture is heated to boiling and combined with 0.6 ml of glacial acetic acid, then a further 2 ml of water are pipetted in. The reaction solution turns dark and is heated for about another half hour until the reaction is complete. The solvent is distilled off using the rotary evaporator, the residue is taken up in methylene chloride and made alkaline with 3 ml of 4N sodium hydroxide solution. The organic phase is separated off and the aqueous phase extracted with methylene chloride. The combined extracts are dried over magnesium sulphate and concentrated by evaporation. The crude product is stirred with a little diethyl ether, suction filtered and washed again. The light grey crystals obtained are dried in the desiccator.
Yield: 350 mg (79 % of theory),
Melting point: 183-189°C
Mass spectrum (ESI^+): m/z = 543, 545 $[M+H]^+$

The following compounds are obtained analogously to Example I:

(1) 6-amino-4-[(3-bromophenyl)amino]-7-(3-{4-[(isopropyloxy-carbonyl)methyl]-piperazin-1-yl}propyloxy)-quinazoline (the reaction is carried out in dioxane instead of ethanol)
Melting point: 188-193°C
Mass spectrum (ESI^+): m/z = 557, 559 $[M+H]^+$

(2) 6-amino-4-[(3-bromophenyl)amino]-7-(3-{4-[(cyclohexyloxy-carbonyl)methyl]-piperazin-1-yl}propyloxy)-quinazoline (the reaction is carried out in dioxane instead of ethanol)

Melting point: 166-169°C
Mass spectrum (ESI^+): m/z = 597, 599 $[M+H]^+$

(3) 6-amino-4-[(3-bromophenyl)amino]-7-(3-{4-[2-(ethoxycarbonyl)ethyl]-piperazin-1-yl}propyloxy)-quinazoline
Melting point: 120-123°C
Mass spectrum (ESI^+): m/z = 557, 559 $[M+H]^+$

(4) 6-amino-4-[(3-bromophenyl)amino]-7-(3-{4-[3-(ethoxycarbonyl)propyl]-piperazin-1-yl}propyloxy)-quinazoline
Melting point: 119-122°C
Mass spectrum (ESI^+): m/z = 571, 573 $[M+H]^+$

(5) 6-amino-4-[(3-bromophenyl)amino]-7-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)-quinazoline
Melting point: 147-161°C
Mass spectrum (ESI^+): m/z = 529, 531 $[M+H]^+$

(6) 6-amino-4-[(3-bromophenyl)amino]-7-({1-[(ethoxycarbonyl)-methyl]-piperidin-4-yl}oxy)-quinazoline
Melting point: 202°C
Mass spectrum (ESI^+): m/z = 500, 502 $[M+H]^+$

(7) 6-amino-4-[(3-bromophenyl)amino]-7-({1-[(ethoxycarbonyl)-methyl]-piperidin-4-yl}methoxy)-quinazoline
Melting point: 155°C
Mass spectrum (ESI^+): m/z = 514, 516 $[M+H]^+$

(8) 6-amino-4-[(3-bromophenyl)amino]-7-(2-{1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}ethoxy)-quinazoline
Melting point: 143°C
Mass spectrum (ESI^+): m/z = 528, 530 $[M+H]^+$

(9) 6-amino-4-[(3-bromophenyl)amino]-7-(3-{1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}propyloxy)-quinazoline
Melting point: 181°C
Mass spectrum (ESI^+): m/z = 542, 544 $[M+H]^+$

(10) 6-amino-4-[(3-bromophenyl)amino]-7-(3-{4-[(diethoxyphosphoryl)methyl]-piperazin-1-yl}propyloxy)-quinazoline
Melting point: 201-205°C
Mass spectrum (ESI^+): m/z = 607, 609 $[M+H]^+$

Example II

4-[(3-bromophenyl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-nitro-quinazoline

292 mg of ethyl bromoacetate are added to 780 mg of 4-[(3-bromophenyl)amino]-7-[3-(piperazin-1-yl)propyloxy]-6-nitro-quinazoline and 0.55 ml of triethylamine in 7 ml of acetonitrile. The reaction mixture is stirred for one hour at ambient temperature, then for about 1.5 hours at 65°C and then for a further 2 days at ambient temperature. As the reaction is incomplete, 2 drops of ethyl bromoacetate are added twice more. The reaction solution is concentrated by evaporation and the residue is partitioned between copious amounts of ethyl acetate and dilute potassium carbonate solution. The organic phase is washed with water and saturated sodium chloride solution, dried over magnesium sulphate and concentrated by evaporation. The yellowish, resin-like crude product is recrystallised from 7 ml of ethanol. The yellow crystals are washed with some cold ethanol and dried in the desiccator.
Yield: 640 mg (70 % of theory),
Melting point: 75°C
Mass spectrum (ESI^+): m/z = 573, 575 $[M+H]^+$

The following compounds are obtained analogously to Example II:

(1) 4-[(3-bromophenyl)amino]-7-(3-{4-[(isopropyloxycarbonyl)-methyl]-piperazin-1-yl}propyloxy)-6-nitro-quinazoline
Melting point: 71-74°C
Mass spectrum (ESI^+): m/z = 587, 589 $[M+H]^+$

(2) 4-[(3-bromophenyl)amino]-7-(3-{4-[(cyclohexyloxycarbonyl)-methyl]-piperazin-1-yl}propyloxy)-6-nitro-quinazoline
Melting point: 80-100°C
Mass spectrum (ESI^+): m/z = 627, 629 $[M+H]^+$

(3) 4-[(3-bromophenyl)amino]-7-(3-{4-[2-(ethoxycarbonyl)ethyl]-piperazin-1-yl}propyloxy)-6-nitro-quinazoline (reaction is carried out with ethyl acrylate in ethanol)
Melting point: 153-156°C
Mass spectrum (ESI^+): m/z = 587, 589 $[M+H]^+$

(4) 4-[(3-bromophenyl)amino]-7-(3-{4-[3-(ethoxycarbonyl)propyl]-piperazin-1-yl}propyloxy)-6-nitro-quinazoline
Melting point: 50-58°C
Mass spectrum (ESI^+): m/z = 601, 603 $[M+H]^+$

(5) 4-[(3-bromophenyl)amino]-7-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)-6-nitro-quinazoline
Melting point: 103-120°C
Mass spectrum (ESI^+): m/z = 559, 561 $[M+H]^+$

(6) 4-[(3-bromophenyl)amino]-7-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}oxy)-6-nitro-quinazoline
Melting point: 151°C
Mass spectrum (ESI^+): m/z = 530, 532 $[M+H]^+$

(7) 4-[(3-bromophenyl)amino]-7-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}methoxy)-6-nitro-quinazoline
Melting point: 189°C
Mass spectrum (ESI^+): m/z = 544, 546 $[M+H]^+$

(8) 4-[(3-bromophenyl)amino]-7-(2-{1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}ethoxy)-6-nitro-quinazoline
Melting point: 185-187°C
Mass spectrum (ESI^+): m/z = 558, 560 $[M+H]^+$

(9) 4-[(3-bromophenyl)amino]-7-(3-{1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}propyloxy)-6-nitro-quinazoline
Melting point: 101°C
Mass spectrum (ESI$^+$): m/z = 572, 574 $[M+H]^+$

Example III

4-[(3-bromophenyl)amino]-6-nitro-7-[3-(piperazin-1-yl)propyl-oxyl-quinazoline

15 ml of trifluoroacetic acid are added dropwise to a suspension of 7.05 g of 4-[(3-bromophenyl)amino]-6-nitro-7-{3-[4-(*tert.* butyloxycarbonyl)-piperazin-1-yl]propyloxy}-quinazoline in 80 ml of methylene chloride at ambient temperature with stirring. While gas is given off, a dark solution is rapidly formed which is stirred for approximately a further 1.5 hours at ambient temperature. The reaction solution is concentrated by evaporation using the rotary evaporator. The resin-like residue is taken up in methylene chloride, combined with ice water and carefully made alkaline with 4N sodium hydroxide solution. Partially precipitated product is dissolved by the addition of more methylene chloride and methanol. The aqueous phase is separated off and extracted with methylene chloride/methanol (9:1). The combined extracts are washed with water, dried over magnesium sulphate and concentrated by evaporation. The crude product is heated to boiling with 25 ml of tert. butylmethylether, cooled with stirring and suction filtered. The yellow crystals thus obtained are washed with diethylether and dried.
Yield: 5.16 g (88 % of theory),
Melting point: 179-182°C
Mass spectrum (ESI$^+$): m/z = 487, 489 $[M+H]^+$

The following compounds are obtained analogously to Example III:

(1) 4-[(3-bromophenyl)amino]-6-nitro-7-[2-(piperazin-1-yl)ethoxy]-quinazoline
Melting point: 133-136°C
Mass spectrum (ESI$^+$): m/z = 473, 475 $[M+H]^+$

(2) 4-[(3-bromophenyl)amino]-6-nitro-7-[(piperidin-4-yl)oxy]-quinazoline
Melting point: 131°C
Mass spectrum (ESI$^+$): m/z = 444, 446 $[M+H]^+$

(3) 4-[(3-bromophenyl)amino]-6-nitro-7-[(piperidin-4-yl)methoxy]-quinazoline
Melting point: 145°C
Mass spectrum (ESI$^+$): m/z = 458, 460 $[M+H]^+$

(4) 4-[(3-bromophenyl)amino]-6-nitro-7-[2-(piperidin-4-yl)ethoxy]-quinazoline
Melting point: 228°C
Mass spectrum (ESI$^+$): m/z = 472, 474 $[M+H]^+$

(5) 4-[(3-bromophenyl)amino]-6-nitro-7-[3-(piperidin-4-yl)propyloxy]-quinazoline
Melting point: 194°C
Mass spectrum (ESI$^+$): m/z = 486, 488 $[M+H]^+$

Example IV

4-[(3-bromophenyl)amino]-6-nitro-7-{3-[4-(tert-butyloxycarbonyl)-piperazin-1-yl]propyloxy}-quinazoline

1.08 g sodium hydride are added to a solution of 6.35 g of 3-[4-(tert. butyloxycarbonyl)-piperazin-1-yl]-propan-1-ol in 100 ml of tetrahydrofuran under a nitrogen atmosphere. The suspension is stirred for about 10 minutes at ambient temperature, then 4.72 g of 4-[(3-bromophenyl)amino]-7-fluoro-6-nitro-quinazoline in 20 ml of tetrahydrofuran are added thereto. The reaction mixture turns dark reddish-brown, while giving off gas, and is gently refluxed for about 25 minutes.

Since only a partial reaction has taken place, a further 0.52 g of sodium hydride are added. The reaction mixture is heated for a further 40 minutes until the reaction has ended. The cooled reaction solution is poured onto about 250 ml of ice-water and neutralised with a little citric acid. The partially precipitated product is extracted with ethyl acetate. The combined extracts are washed with a little water, followed by saturated sodium chloride solution, dried over magnesium sulphate and concentrated by evaporation. 11.30 g of crude product is obtained as a dark resin which is heated to boiling with 25 ml of methanol with stirring, whereupon the product crystallises out. The suspension is cooled with ice water and suction filtered. The brownish-yellow crystals obtained are washed again with 10 ml of cold methanol and dried in the desiccator.
Yield: 7.08 g (92 % of theory),
Melting point: 152-156°C
Mass spectrum (ESI^+): m/z = 587, 589 $[M+H]^+$

The following compounds are obtained analogously to Example IV:

(1) 4-[(3-bromophenyl)amino]-6-nitro-7-{2-[4-(tert-butyloxycarbonyl)-piperazin-1-yl]ethoxy}-quinazoline
Melting point: 219-222°C
Mass spectrum (ESI^+): m/z = 573, 575 $[M+H]^+$

(2) 4-[(3-bromophenyl)amino]-6-nitro-7-{[1-(tert-butyloxycarbonyl)-piperidin-4-yl]oxy}-quinazoline
Melting point: 190°C
Mass spectrum (ESI^-): m/z = 542, 544 $[M-H]^-$

(3) 4-[(3-bromophenyl)amino]-6-nitro-7-{[1-(tert-butyloxycarbonyl)-piperidin-4-yl]methoxy}-quinazoline
Melting point: 240°C
Mass spectrum (ESI^+): m/z = 558, 560 $[M+H]^+$

(4) 4-[(3-bromophenyl)amino]-6-nitro-7-{2-[1-(tert-butyloxycarbonyl)-piperidin-4-yl]ethoxy}-quinazoline
Melting point: 208°C
Mass spectrum (ESI^+): m/z = 572, 574 $[M+H]^+$

(5) 4-[(3-bromophenyl)amino]-6-nitro-7-{3-[1-(tert-butyloxycarbonyl)-piperidin-4-yl]propyloxy}-quinazoline
Melting point: 203°C
Mass spectrum (ESI^-): m/z = 584, 586 $[M-H]^-$

Example V

4-[(3-bromophenyl)amino]-6-[(4-bromo-1-oxo-2-buten-1-yl)amino]-quinazoline

1.74 ml of oxalylchloride and one drop of dimethylformamide are added to a solution of 1.65 g of 4-bromo-2-butenoic acid in 15 ml of methylene chloride at ambient temperature. The reaction mixture is stirred for about one hour at ambient temperature until the development of gas has ceased. The acid chloride formed is largely freed from the solvent *in vacuo* using the rotary evaporator. The oily brown crude product is taken up in 25 ml of tetrahydrofuran and added dropwise, while cooling with a ice bath, to a solution of 3.15 g of 4-[(3-bromophenyl)amino]-6-amino-quinazoline and 2.30 ml of Hünig base in 25 ml of tetrahydrofuran. The reaction mixture is stirred for 30 minutes while cooling with ice and then stirred for another 1.5 hours at ambient temperature. For working up, 25 ml of water and 50 ml of ethyl acetate are added. The organic phase is separated off, washed with saturated sodium chloride solution, dried over magnesium sulphate and concentrated by evaporation. The residue is boiled in 30 ml of ethyl acetate to purify it further and filtered while hot. The yellow crystalline product is washed with hot ethyl acetate and dried.
Yield: 3.00 g (65 % of theory),

R_f value: 0.33 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 9:1:0.1)
Mass spectrum (ESI$^+$): m/z = 463 $[M+H]^+$

The following compound is obtained analogously to Example V:

(1) 4-[(3-bromophenyl)amino]-6-[(4-bromo-1-oxo-2-buten-1-yl)-amino]-7-methoxy-quinazoline

Example VI

3-{N-[(ethoxycarbonyl)methyl]-N-methylamino}propylamin-hydrochloride

20 ml of trifluoroacetic acid are added dropwise to a solution of 6.10 g of N-[3-(tert. butyloxycarbonylamino)-propyl]-sarcosine ethyl ester in 40 ml of methylene chloride whilst cooling with an ice bath. The reaction mixture is then stirred for about another three hours at 0°C until the evaluation of gas has ended. For working up, the solvent is largely distilled off *in vacuo* in the rotary evaporator. The residue is taken up in ethereal hydrochloric acid solution and again evaporated to dryness.
Yield: 4.72 g (86 % of theory),
R_f value: 0.80 (silica gel, acetonitrile/water/trifluoroacetic acid = 50:50:1)
Mass spectrum (EI): m/z = 174 $[M]^+$

Example VII

N-[3-(tert-butyloxycarbonylamino)-propyl]-sarcosine ethyl ester

A solution of 17.90 g 3-(tert. butyloxycarbonylamino)propyl bromide in 50 ml of acetonitrile is added dropwise to a mixture of 11.55 g of sarcosine ethylester hydrochloride and 28.8 ml of Hünig base in 200 ml of acetonitrile within 30 minutes while cooling with an ice bath. The reaction mixture

is allowed to come up to ambient temperature overnight in the ice bath. Then the solvent is distilled off using the rotary evaporator, the residue is taken up in tert-butyl-methylether and washed with ice water. The organic phase is dried over magnesium sulphate and concentrated by evaporation. The crude product is chromatographed on a silica gel column with methylene chloride/methanol/concentrated aqueous ammonia solution (100:2:0.1).
Yield: 20.62 g (30 % of theory),
R_f value: 0.50 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 20:1:0.1)
Mass spectrum (ESI^+): m/z = 275 $[M+H]^+$

Example VIII

4-[(3-bromophenyl)amino]-7-(3-{4-[(diethoxyphosphoryl)methyl]-piperazin-1-yl}propyloxy)-6-nitro-quinazoline

0.08 ml of a 37% formaldehyde solution is added to a suspension of 487 mg of 4-[(3-bromophenyl)amino]-6-nitro-7-[3-(piperazin-1-yl)propyloxy]-quinazoline in 3 ml of dioxane. The suspension is briefly heated in an oil bath until a clear solution is obtained. Then 0.16 ml of diethylphosphite are pipetted in with stirring at ambient temperature. The reaction mixture is then stirred for a further half hour at ambient temperature, then heated to 90-100°C in an oil bath. After another three hours the reaction is complete. The reaction solution is concentrated by evaporation, the residue is stirred with ice-water, filtered off and dried in the desiccator. The crude product is purified by chromatography over a silica gel column with methylene chloride/ethanol (9:1).
Yield: 540 mg (85 % of theory),
Melting point: 140-143°C
Mass spectrum (ESI^+): m/z = 637, 639 $[M+H]^+$

Preparation of the end products:

Example 1

4-[(3-bromophenyl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline

440 mg of 6-amino-4-[(3-bromophenyl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-quinazoline are suspended in 20 ml of methylene chloride at ambient temperature and combined with 0.24 ml of triethylamine under a nitrogen atmosphere. The reaction mixture is cooled to -10°C with an ice/sodium chloride bath, then a solution of 84 mg of acrylic acid chloride in 5 ml of methylene chloride is added dropwise within about 10 minutes. After another 10 minutes the reaction is complete. The reaction solution is washed with a little dilute potassium carbonate solution and water, dried and concentrated by evaporation. 526 mg of crude product are obtained as a brown resin which is purified by chromatography on a silica gel column with methylene chloride/ethanol (95:5).
Yield: 300 mg (62 % of theory),
Melting point: 110-113°C
Mass spectrum (ESI^+): m/z = 597, 599 $[M+H]^+$

The following compounds are obtained analogously to Example 1:

(1) 4-[(3-bromophenyl)amino]-7-(3-{4-[(isopropyloxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline
Melting point: 95-100°C
Mass spectrum (ESI^+): m/z = 611, 613 $[M+H]^+$

(2) 4-[(3-bromophenyl)amino]-7-(3-{4-[(cyclohexyloxycarbonyl)-methyl]-piperazin-1-yl}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline
Melting point: 96-104°C
Mass spectrum (ESI^+): m/z = 651, 653 $[M+H]^+$

(3) 4-[(3-bromophenyl)amino]-7-(3-{4-[2-(ethoxycarbonyl)ethyl]-piperazin-1-yl}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline
Melting point: 97-102°C
Mass spectrum (ESI^+): m/z = 611, 613 $[M+H]^+$

(4) 4-[(3-bromophenyl)amino]-7-(3-{4-[3-(ethoxycarbonyl)propyl]-piperazin-1-yl}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline
Melting point: 107-111°C
Mass spectrum (ESI^+): m/z = 625, 627 $[M+H]^+$

(5) 4-[(3-bromophenyl)amino]-7-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)-6-[(vinylcarbonyl)amino]-quinazoline
Melting point: 75-79°C
Mass spectrum (ESI^+): m/z = 583, 585 $[M+H]^+$

(6) 4-[(3-bromophenyl)amino]-7-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}oxy)-6-[(vinylcarbonyl)amino]-quinazoline
Melting point: 95°C
Mass spectrum (ESI^+): m/z = 554, 556 $[M+H]^+$

(7) 4-[(3-bromophenyl)amino]-7-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}methoxy)-6-[(vinylcarbonyl)amino]-quinazoline
Melting point: 141°C
Mass spectrum (ESI^+): m/z = 568, 570 $[M+H]^+$

(8) 4-[(3-bromophenyl)amino]-7-(2-{1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}ethoxy)-6-[(vinylcarbonyl)amino]-quinazoline
Melting point: 156°C
Mass spectrum (ESI^+): m/z = 582, 584 $[M+H]^+$

(9) 4-[(3-bromophenyl)amino]-7-(3-{1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline
Melting point: 124°C
Mass spectrum (ESI^+): m/z = 596, 598 $[M+H]^+$

(10) 4-[(3-bromophenyl)amino]-7-(3-{4-[(diethoxyphosphoryl)-methyl]-piperazin-1-yl}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline
Melting point: 80-85°C
Mass spectrum (ESI$^+$): m/z = 661, 663 $[M+H]^+$

(11) 4-[(3-bromophenyl)amino]-7-(3-{4-[(diethoxyphosphoryl)-methyl]-piperazin-1-yl}propyloxy)-6-[(1-oxo-2-butyn-1-yl)amino]-quinazoline (the reaction is carried out with 2-butinecarboxylic acid and isobutyl chloroformate in tetrahydrofuran)
Melting point: 137-139°C
Mass spectrum (ESI$^+$): m/z = 673, 675 $[M+H]^+$

Example 2

4-[(3-bromophenyl)amino]-6-[(4-{N-[(ethoxycarbonyl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-quinazoline

13.94 ml of Hünig base are pipetted into a suspension of 9.37 g of sarcosine ethylester hydrochloride in 25 ml of tetrahydrofuran while cooling with an ice bath. Then a solution of 2.00 g of 4-[(3-bromophenyl)amino]-6-[(4-bromo-1-oxo-2-buten-1-yl)amino]-quinazoline in 10 ml of dimethylformamide is added dropwise within 15 minutes. The reaction mixture is allowed to come up to ambient temperature overnight in an ice bath. For working up, 25 ml of saturated sodium hydrogen carbonate solution and 50 ml of ethyl acetate are added. The organic phase is separated off and the aqueous phase is extracted with ethyl acetate. The combined organic phases are washed with saturated sodium chloride solution, dried over magnesium sulphate and concentrated by evaporation. The dark-brown oily residue is stirred with 50 ml of water, the precipitate formed is suction filtered and washed with water. The crude product is purified by chromatography on a silica gel column with methylene chloride/methanol (50:1 to 20:1).

Yield: 1.00 g (46 %of theory),
Melting point: 182-183°C
Mass spectrum (ESI^-): m/z = 496, 498 $[M-H]^-$

The following compounds are obtained analogously to Example 2:

(1) 4-[(3-bromophenyl)amino]-6-[(4-{N-[(ethoxycarbonyl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline
Melting point: 121-125°C
Mass spectrum (EI): m/z = 527, 529 $[M]^+$

(2) 4-[(3-bromophenyl)amino]-6-[(4-{N,N-bis[(ethoxycarbonyl)methyl]-amino}-1-oxo-2-buten-1-yl)amino]-quinazoline
Melting point: 150-154°C
Mass spectrum (EI): m/z = 541, 543 $[M]^+$

(3) 4-[(3-bromophenyl)amino]-6-({4-[2-(methoxycarbonyl)-pyrrolidin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-methoxy-quinazoline
R_f value: 0.43 (silica gel, methylene chloride/methanol = 9:1)
Mass spectrum (ESI^+): m/z = 539, 541 $[M+H]^+$

(4) 4-[(3-bromophenyl)amino]-6-[(4-{N-[(diethoxyphosphoryl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline
R_f value: 0.38 (silica gel, methylene chloride/methanol = 9:1)
Mass spectrum (ESI^-): m/z = 590, 592 $[M-H]^-$

(5) 4-[(3-bromophenyl)amino]-6-[(4-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline
R_f value: 0.37 (silica gel, methylene chloride/methanol = 9:1)
Mass spectrum (ESI^+): m/z = 553, 555 $[M+H]^+$

Example 3

4-[(3-bromophenyl)amino]-6-{[4-(3-{N-[(ethoxycarbonyl)methyl]-N-methylamino}propylamino)-1,4-dioxo-2-buten-1-yl]amino}-quinazoline

106 mg of benzotriazol-1-yl-N-tetramethyl-uronium-tetrafluoroborate and 68 mg of 1-hydroxybenzotriazole are added to a solution of 200 mg of 4-[(3-bromophenyl)amino]-6-{[(2-carboxy-vinyl)carbonyl]amino}-quinazoline in 2.5 ml of dimethyl-formamide. The solution is stirred for 20 minutes at ambient temperature, then 0.5 ml of Hünig's base and 148 mg of 3-{N-[(ethoxycarbonyl)methyl]-N-methylamino}propylamine, dissolved in 0.5 ml of dimethylformamide, are added. The reaction mixture is stirred for a further two hours at ambient temperature before being poured onto 50 ml of water for working up. The aqueous phase is extracted with ethyl acetate, the combined organic phases are washed with saturated sodium chloride solution, dried over magnesium sulphate and concentrated by evaporation. The crude product is purified by chromatography o a silica gel column with methylene chloride/ethanol (20:1 to 9:1).
Yield: 106 mg (39 % of theory),
Melting point: 278-279°C
Mass spectrum (ESI^+): m/z = 569, 571 $[M+H]^+$

Example 4

4-[(3-bromophenyl)amino]-6-({4-[(tert-butylcarbonyloxy)methoxyl-1,4-dioxo-2-buten-1-yl}amino)-7-methoxy-quinazoline

207 mg of potassium carbonate and 0.144 ml of chloromethyl pivalate are added to 200 mg of 4-[(3-bromophenyl)amino]-6-{[(2-carboxy-vinyl)carbonyl]amino}-quinazoline in 2 ml of dimethylsulphoxide. Then a further 30 mg of sodium iodide are added and the reaction mixture is stirred for 48 hours at ambient temperature. For working up, the reaction mixture is diluted with 20 ml of water and extracted with ethyl acetate. The combined extracts are washed with saturated sodium chloride solution, dried over magnesium sulphate and concentrated by evaporation. The crude product mixture is

purified by chromatography on a silica gel column with methylene chloride/methanol (20:1).
Yield: 10 mg (4 % of theory),
R_f value: 0.42 (silica gel, methylene chloride/methanol = 9:1)
Mass spectrum (EI): m/z = 526 $[M]^+$

The following compound is obtained analogously to Example 4:

(1) 4-[(3-bromophenyl)amino]-6-({4-[1-(ethyloxycarbonyloxy)-ethoxy]-1,4-dioxo-2-buten-1-yl}amino)-7-methoxy-quinazoline
(the reaction is carried out in dimethylformamide)
R_f value: 0.43 (silica gel, methylene chloride/methanol = 9:1)
Mass spectrum (ESI$^+$): m/z = 529, 531 $[M+H]^+$

The following compounds may also be obtained analogously to the preceding Examples and other methods known from the literature:

(1) 4-[(3-bromophenyl)amino]-7-(3-{4-[(butyloxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline

(2) 4-[(3-bromophenyl)amino]-7-(3-{4-[(diethoxyphosphoryl)-methyl]-piperazin-1-yl}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline

(3) 4-[(3-bromophenyl)amino]-7-[(ethoxycarbonyl)methoxy]-6-[(vinylcarbonyl)amino]-quinazoline

(4) 4-[(3-bromophenyl)amino]-7-[2-(ethoxycarbonyl)ethoxy]-6-[(vinylcarbonyl)amino]-quinazoline

(5) 4-[(3-bromophenyl)amino]-7-[3-(ethoxycarbonyl)propyloxy]-6-[(vinylcarbonyl)amino]-quinazoline

(6) 4-[(3-bromophenyl)amino]-7-(2-{N-[(ethoxycarbonyl)methyl]-N-methylamino}ethoxy)-6-[(vinylcarbonyl)amino]-quinazoline

(7) 4-[(3-bromophenyl)amino]-7-(3-{N-[(ethoxycarbonyl)methyl]-N-methylamino}propyloxy)-[(vinylcarbonyl)amino]-quinazoline

(8) 4-[(3-bromophenyl)amino]-7-(4-{N-[(ethoxycarbonyl)methyl]-N-methylamino}butyloxy)-6-[(vinylcarbonyl)amino]-quinazoline

(9) 4-[(3-bromophenyl)amino]-7-{3-[4-(carboxymethyl)-piperazin-1-yl]propyloxy}-6-[(vinylcarbonyl)amino]-quinazoline

(10) 4-[(3-bromophenyl)amino]-7-(3-{4-[(diethoxyphosphoryl)methyl]-piperazin-1-yl}propyloxy)-6-[(1-oxo-2-butyn-1-yl)amino]-quinazoline

(11) 4-[(3-bromophenyl)amino]-6-[(4-{N-[(methoxycarbonyl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(12) 4-[(3-bromophenyl)amino]-6-[(4-{N-[(propyloxycarbonyl)-methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(13) 4-[(3-bromophenyl)amino]-6-[(4-{N-[(isobutyloxycarbonyl)-methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(14) 4-[(3-bromophenyl)amino]-6-[(4-{N-[(cyclohexyl-oxycarbonyl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(15) 4-[(3-bromophenyl)amino]-6-[(4-{N-[(hexyloxycarbonyl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(16) 4-[(3-bromophenyl)amino]-6-[(4-{N-[(cyclopropylmethoxy-carbonyl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(17) 4-[(3-bromophenyl)amino]-6-[(4-{N-[(cyclohexylmethoxy-carbonyl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(18) 4-[(3-bromophenyl)amino]-6-[(4-{N-[(benzyloxy-carbonyl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(19) 4-[(3-bromophenyl)amino]-6-[(4-{N-[(ethoxycarbonyl)methyl]-N-ethylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(20) 4-[(3-bromophenyl)amino]-6-[(4-{N-[(ethoxycarbonyl)methyl]-N-butylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(21) 4-[(3-bromophenyl)amino]-6-[(4-{N-[(ethoxycarbonyl)methyl]-N-cyclopropylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(22) 4-[(3-bromophenyl)amino]-6-[(4-{N-[(ethoxycarbonyl)methyl]-N-(cyclopropylmethyl)amino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(23) 4-[(3-bromophenyl)amino]-6-[(4-{N-[2-(ethoxycarbonyl)-ethyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(24) 4-[(3-bromophenyl)amino]-6-[(4-{N-[3-(ethoxycarbonyl)-propyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(25) 4-[(3-bromophenyl)amino]-6-[(4-{N-[1-(ethoxycarbonyl)-ethyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(26) 4-[(3-bromophenyl)amino]-6-({4-[2-(ethoxycarbonyl)-pyrrolidin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-methoxy-quinazoline

(27) 4-[(3-bromophenyl)amino]-6-({4-[4-(ethoxycarbonyl)-piperidin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-methoxy-quinazoline

(28) 4-[(3-bromophenyl)amino]-6-[(4-{4-[(ethoxycarbonyl)methyl]-piperidin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(29) 4-[(3-bromophenyl)amino]-6-[(4-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(30) 4-[(3-bromophenyl)amino]-6-[(6-{N-[(ethoxycarbonyl)methyl]-N-methylamino}-1-oxo-2-hexen-1-yl)amino]-7-methoxy-quinazoline

(31) 4-[(3-bromophenyl)amino]-6-[(3-{1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}-1-oxo-2-propen-1-yl)amino]-7-methoxy-quinazoline

(32) 4-[(3-bromophenyl)amino]-6-({4-[3-(ethoxycarbonyl)-4-methyl-piperazin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-methoxy-quinazoline

(33) 4-[(3-bromophenyl)amino]-6-[(4-{N-[(diethoxyphosphoryl)-methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(34) 4-[(3-bromophenyl)amino]-6-[(4-{N-[(ethoxycarbonyl)methyl]-N-methylamino}-1-oxo-2-butyn-1-yl)amino]-7-methoxy-quinazoline

(35) 4-[(3-bromophenyl)amino]-6-[(4-{N-[2-(ethoxycarbonyl)-ethyl]-N-methylamino}-1-oxo-2-butyn-1-yl)amino]-7-methoxy-quinazoline

(36) 4-[(3-bromophenyl)amino]-6-[(4-{N-[3-(ethoxycarbonyl)-propyl]-N-methylamino}-1-oxo-2-butyn-1-yl)amino]-7-methoxy-quinazoline

(37) 4-[(3-bromophenyl)amino]-6-({4-[(isopropylcarbonyloxy)-methoxy]-1,4-dioxo-2-buten-1-yl}amino)-7-methoxy-quinazoline

(38) 4-[(3-bromophenyl)amino]-6-({4-[(methylcarbonyloxy)methoxy]-1,4-dioxo-2-buten-1-yl}amino)-7-methoxy-quinazoline

(39) 4-[(3-bromophenyl)amino]-6-({4-[(tert. butylcarbonyloxy)-methoxy]-1,4-dioxo-2-buten-1-yl}amino)-7-methoxy-quinazoline

(40)4-[(3-bromophenyl)amino]-6-({4-[1-(ethyloxycarbonyloxy)-ethoxy]-1,4-dioxo-2-buten-1-yl}amino)-7-methoxy-quinazoline

(41) 4-[(3-bromophenyl)amino]-6-({4-[1-(cyclohexyloxycarbonyl-oxy)ethoxy]-1,4-dioxo-2-buten-1-yl}amino)-7-methoxy-quinazoline

(42) 4-[(3-bromophenyl)amino]-6-{[4-(2-{N-[(ethoxycarbonyl)-methyl]-N-methylamino}ethylamino)-1,4-dioxo-2-buten-1-yl]-amino}-7-methoxy-quinazoline

(43) 4-[(3-bromophenyl)amino]-6-{[4-(2-{N-[2-(ethoxycarbonyl)-ethyl]-N-methylamino}ethylamino)-1,4-dioxo-2-buten-1-yl]amino}-7-methoxy-quinazoline

(44) 4-[(3-bromophenyl)amino]-6-{[4-(3-{N-[(ethoxycarbonyl)-methyl]-N-methylamino}propylamino)-1,4-dioxo-2-buten-1-yl]-amino}-7-methoxy-quinazoline

(45) 4-[(3-bromophenyl)amino]-6-{[4-(3-{N-[(methoxycarbonyl)-methyl]-N-methylamino}propylamino)-1,4-dioxo-2-buten-1-yl]-amino}-7-methoxy-quinazoline

(46) 4-[(3-bromophenyl)amino]-6-{[4-(3-{N-[(butyloxycarbonyl)-methyl]-N-methylamino}propylamino)-1,4-dioxo-2-buten-1-yl]-amino}-7-methoxy-quinazoline

(47) 4-[(3-bromophenyl)amino]-6-{[4-(3-{N-[(cyclohexyloxy-carbonyl)methyl]-N-methylamino}propylamino)-1,4-dioxo-2-buten-1-yl]amino}-7-methoxy-quinazoline

(48) 4-[(3-bromophenyl)amino]-6-[(4-{3-[2-(ethoxycarbonyl)-pyrrolidin-1-yl]propylamino}-1,4-dioxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(49) 4-[(3-bromophenyl)amino]-6-[(4-{3-[2-(methoxycarbonyl)-piperidin-1-yl]propylamino}-1,4-dioxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(50) 4-[(3-bromophenyl)amino]-6-[(4-{3-[4-(ethoxycarbonyl)-piperidin-1-yl]propylamino}-1,4-dioxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(51) 4-[(3-bromophenyl)amino]-6-[(4-{3-[3-(ethoxycarbonyl)-piperidin-1-yl]propylamino}-1,4-dioxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(52) 4-[(3-bromophenyl)amino]-6-{[4-(3-{4-[(ethoxycarbonyl)-methyl]-piperazin-1-yl}propylamino)-1,4-dioxo-2-buten-1-yl]-amino}-7-methoxy-quinazoline

(53) 4-[(3-bromophenyl)amino]-6-{[4-(3-{4-[(ethoxycarbonyl)-methyl]-piperazin-1-yl}propylamino)-1,4-dioxo-2-buten-1-yl]-amino}-quinazoline

(54) 4-[(3-bromophenyl)amino]-6-[(4-{3-[2-(ethoxycarbonyl)-pyrrolidin-1-yl]propylamino}-1,4-dioxo-2-buten-1-yl)amino]-quinazoline

(55) 4-[(3-bromophenyl)amino]-6-{[4-(N-{1-[(ethoxycarbonyl)methyl]-2-(ethoxycarbonyl)-ethyl}-N-methylamino)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline

(56) 4-[(3-bromophenyl)amino]-6-[(4-{N-[1,2-bis(ethoxycarbonyl)-ethyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(57) 4-[(3-bromophenyl)amino]-6-{[4-(N-{[(ethoxy)(methyl)-phosphoryl]methyl}-N-methylamino)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline

(58) 4-[(3-bromophenyl)amino]-6-({4-[N-({[1-(propylcarbonyl-oxy)-3-methyl-butyloxy](methyl)phosphoryl}methyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-methoxy-quinazoline

(59) 4-[(3-bromophenyl)amino]-6-({4-[N-({[1-(ethylcarbonyloxy)-2-methyl-propyloxy](methyl)phosphoryl}methyl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-methoxy-quinazoline

(60) 4-[(3-bromophenyl)amino]-6-({4-[N-({bis[(isopropylcarbonyloxy)methoxy]-phosphoryl}methyl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-methoxy-quinazoline

(61) 4-[(3-bromophenyl)amino]-7-(3-{N-[(isobutyloxycarbonyl)methyl]-N-methylamino}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline

(62) 4-[(3-bromophenyl)amino]-7-(3-{N-[(cyclopentyloxycarbon-yl)methyl]-N-methylamino}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline

(63) 4-[(3-bromophenyl)amino]-7-{3-[2-(ethoxycarbonyl)-pyrrolidin-1-yl]propyloxy}-6-[(vinylcarbonyl)amino]-quinazoline

(64) 4-[(3-bromophenyl)amino]-7-{3-[2-(ethoxycarbonyl)-piperidin-1-yl]propyloxy}-6-[(vinylcarbonyl)amino]-quinazoline

(65) 4-[(3-bromophenyl)amino]-7-(3-{N-[1-(ethoxycarbonyl)-ethyl]-N-methylamino}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline

(66) 4-[(3-bromophenyl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-[(1-oxo-2-buten-1-yl)amino]-quinazoline

(67) 4-[(3-bromophenyl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-[(1-oxo-2,4-hexadien-1-yl)amino]-quinazoline

(68) 4-[(3-bromophenyl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-[(3-phenyl-1-oxo-2-propen-1-yl)-amino]-quinazoline

(69) 4-[(3-bromophenyl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-[(1-oxo-2-butyn-1-yl)amino]-quinazoline

(70) 4-[(3-bromophenyl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-[(1-oxo-4,4,4-trifluoro-2-buten-1-yl)amino]-quinazoline

(71) 4-[(3-bromophenyl)amino]-7-(3-{N-[(ethoxycarbonyl)methyl]-N-methylamino}propyloxy)-6-[(1-oxo-4,4,4-trifluoro-2-buten-1-yl)amino]-quinazoline

(72) 4-[(3-bromophenyl)amino]-7-(3-{N-[(ethoxycarbonyl)methyl]-N-methylamino}propyloxy)-[(1-oxo-2-buten-1-yl)amino]-quinazoline

(73) 4-[(3-bromophenyl)amino]-7-(3-{N-[(ethoxycarbonyl)methyl]-N-methylamino}propyloxy)-[(1-oxo-2-butyn-1-yl)amino]-quinazoline

(74) 4-[(3-bromophenyl)amino]-7-(3-{N-[(ethoxycarbonyl)methyl]-N-methylamino}propyloxy)-[(1-oxo-2,4-hexadien-1-yl)amino]-quinazoline

(75) 4-[(3-bromophenyl)amino]-6-{[2-({N-[(ethoxycarbonyl)methyl]-N-methylamino}methyl)-1-oxo-2-propen-1-yl]amino}-7-methoxy-quinazoline

(76) 4-[(3-bromophenyl)amino]-6-{[2-({N-[(ethoxycarbonyl)methyl]-N-methylamino}methyl)-1-oxo-2-propen-1-yl]amino}-quinazoline

(77) 4-[(3-chlorophenyl)amino]-6-[(4-{N-[(ethoxycarbonyl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(78) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{N-[(ethoxycarbonyl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(79) 4-[(3-methylphenyl)amino]-6-[(4-{N-[(ethoxycarbonyl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(80) 4-[(3-trifluoromethylphenyl)amino]-6-[(4-{N-[(ethoxycarbonyl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(81) 4-[(3-ethinylphenyl)amino]-6-[(4-{N-[(ethoxycarbonyl)-methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(82) 4-[(3-cyanophenyl)amino]-6-[(4-{N-[(ethoxycarbonyl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(83) 4-[(3-methoxyphenyl)amino]-6-[(4-{N-[(ethoxycarbonyl)-methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(84) 4-[(3,4-difluorophenyl)amino]-6-[(4-{N-[(ethoxycarbonyl)-methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(85) 4-[(3-bromine-4-fluorophenyl)amino]-6-[(4-{N-[(ethoxycarbonyl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline

(86) 4-[(3-chlorophenyl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline

(87) 4-[(3-chloro-4-fluorophenyl)amino]-7-(3-{4-[(ethoxy-carbonyl)methyl]-piperazin-1-yl}propyloxy)-6-[(vinylcarbonyl)-amino]-quinazoline

(88) 4-[(3-bromine-4-fluorophenyl)amino]-7-(3-{4-[(ethoxy-carbonyl)methyl]-piperazin-1-yl}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline

(89) 4-[(3,4-difluorophenyl)amino]-7-(3-{4-[(ethoxycarbonyl)-methyl]-piperazin-1-yl}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline

(90) 4-[(3-cyanophenyl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline

(91) 4-[(3-methoxyphenyl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline

(92) 4-[(3-methylphenyl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline

(93) 4-[(3-trifluoromethylphenyl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline

(94) 4-[(3-ethinylphenyl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline

(95) 4-[(3-bromophenyl)amino]-3-cyano-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-[(vinylcarbonyl)amino]-quinoline

(96) 4-[(3-bromophenyl)amino]-3-cyano-7-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)-6-[(vinylcarbonyl)amino]-quinoline

(97) 4-[(3-bromophenyl)amino]-3-cyano-7-(3-{1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}propyloxy)-6-[(vinylcarbonyl)amino]-quinoline

(98) 4-[(3-bromophenyl)amino]-3-cyano-7-(2-{1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}ethoxy)-6-[(vinylcarbonyl)amino]-quinoline

(99) 4-[(3-bromophenyl)amino]-3-cyano-7-({1-[(ethoxycarbonyl)-methyl]-piperidin-4-yl}methoxy)-6-[(vinylcarbonyl)amino]-quinoline

(100) 4-[(3-bromophenyl)amino]-3-cyano-7-(3-{N-[(ethoxy-carbonyl)methyl]-N-methylamino}propyloxy)-6-[(vinylcarbonyl)amino]-quinoline

(101) 4-[(3-bromophenyl)amino]-3-cyano-7-(4-{N-[(ethoxy-carbonyl)methyl]-N-methylamino}butyloxy)-6-[(vinylcarbonyl)amino]-quinoline

(102) 4-[(3-bromophenyl)amino]-3-cyano-6-[(4-{N-[(ethoxy-carbonyl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-quinoline

(103) 4-[(3-bromophenyl)amino]-3-cyano-6-[(4-{N-[(ethoxy-carbonyl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinoline

(104) 4-[(3-bromophenyl)amino]-3-cyano-6-[(4-{N-[(ethoxy-carbonyl)methyl]-N-ethylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinoline

(105) 4-[(3-bromophenyl)amino]-3-cyano-6-[(4-{N,N-bis[(ethoxy-carbonyl)methyl]amino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinoline

(106) 4-[(3-bromophenyl)amino]-3-cyano-6-({4-[2-(ethoxy-carbonyl)-pyrrolidin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-methoxy-quinoline

(107) 4-[(3-bromophenyl)amino]-3-cyano-6-[(4-{4-[(ethoxy-carbonyl)methyl]-piperidin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinoline

(108) 4-[(3-bromophenyl)amino]-3-cyano-6-[(4-{N-[(diethoxy-phosphoryl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinoline

(109) 4-[(3-bromophenyl)amino]-3-cyano-6-({4-[N-({bis[(iso-propyl-carbonyloxy)methoxy]-phosphoryl}methyl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-methoxy-quinoline

(110) 4-[(3-bromophenyl)amino]-3-cyano-6-{[4-(N-{[(ethoxy)(methyl)phosphoryl]methyl}-N-methylamino)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinoline

(111) 4-[(3-bromophenyl)amino]-3-cyano-6-({4-[N-({[1-(ethyl-carbonyloxy)-2-methyl-propyloxy](methyl)phosphoryl}methyl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-methoxy-quinoline

(112) 4-[(3-bromophenyl)amino]-3-cyano-6-({4-[N-({[1-(ethyl-carbonyloxy)ethoxy](methyl)phosphoryl}methyl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-methoxy-quinoline

(113) 4-[(3-bromophenyl)amino]-3-cyano-6-[(4-{N-[(ethoxycarbonyl)methyl]-N-methylamino}-1-oxo-2-butyn-1-yl)amino]-7-methoxy-quinoline

(114) 4-[(3-bromophenyl)amino]-3-cyano-6-{[2-({N-[(ethoxy-carbonyl)methyl]-N-methylamino}methyl)-1-oxo-2-propen-1-yl]amino}-7-methoxy-quinoline

(115) 4-[(3-bromophenyl)amino]-3-cyano-6-{[4-(3-{N-[(ethoxy-carbonyl)methyl]-N-methylamino}propylamino)-1,4-dioxo-2-buten-1-yl]amino}-7-methoxy-quinoline

(116) 4-[(3-bromophenyl)amino]-3-cyano-6-{[4-(3-{N,N-bis[(ethoxy-carbonyl)methyl]-amino}propylamino)-1,4-dioxo-2-buten-1-yl]amino}-7-methoxy-quinoline

(117) 4-[(3-bromophenyl)amino]-3-cyano-6-[(4-{3-[2-(ethoxy-carbonyl)-pyrrolidin-1-yl]propylamino}-1,4-dioxo-2-buten-1-yl)amino]-7-methoxy-quinoline

(118) 4-[(3-bromophenyl)amino]-3-cyano-6-{[4-(3-{4-[(ethoxy-carbonyl)methyl]-piperazin-1-yl}propylamino)-1,4-dioxo-2-buten-1-yl]amino}-7-methoxy-quinoline

(119) 4-[(3-bromophenyl)amino]-3-cyano-6-({4-[(tert-butyl-carbonyloxy)methoxy]-1,4-dioxo-2-buten-1-yl}amino)-7-methoxy-quinoline

(120) 4-[(3-bromophenyl)amino]-3-cyano-6-({4-[1-(ethoxy-carbonyloxy)ethoxy]-1,4-dioxo-2-buten-1-yl}amino)-7-methoxy-quinoline

(121) 4-[(3-bromophenyl)amino]-3-cyano-6-({4-[1-(cyclohexyloxy-carbonyloxy)ethoxy]-1,4-dioxo-2-buten-1-yl}amino)-7-methoxy-quinoline

(122) 4-[(3-bromophenyl)amino]-6-{[4-(2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline

(123) 4-[(3-bromophenyl)amino]-7-[3-(2-oxo-morpholin-4-yl)propyloxy]-6-[(vinylcarbonyl)amino]-quinazoline

(124) 4-[(3-bromophenyl)amino]-7-[3-(2-oxo-morpholin-4-yl)propyloxy]-6-[(1-oxo-2-butyn-1-yl)amino]-quinazoline

(125) 4-[(3-bromophenyl)amino]-7-[(4-methyl-2-oxo-morpholin-6-yl)methyloxy]-6-[(1-oxo-2-butyn-1-yl)amino]-quinazoline

Example 4

Coated tablets containing 75 mg of active substance

1 tablet core contains:

active substance	75.0 mg
calcium phosphate	93.0 mg
corn starch	35.5 mg
polyvinylpyrrolidone	10.0 mg
hydroxypropylmethylcellulose	15.0 mg
magnesium stearate	1.5 mg
	230.0 mg

Preparation:

The active substance is mixed with calcium phosphate, corn starch, polyvinylpyrrolidone, hydroxypropylmethylcellulose and half the specified amount of magnesium stearate. Blanks 13 mm in diameter are produced in a tablet-making machine and these are then rubbed through a screen with a mesh size of 1.5 mm using a suitable machine and mixed with the rest of the magnesium stearate. This granulate is compressed in a tablet-making machine to form tablets of the desired shape.

Weight of core: 230 mg
die: 9 mm, convex

The tablet cores thus produced are coated with a film consisting essentially of hydroxypropylmethylcellulose. The finished film-coated tablets are polished with beeswax.

Weight of coated tablet: 245 mg.

Example 5

Tablets containing 100 mg of active substance

Composition:
1 tablet contains:

active substance	100.0 mg
lactose	80.0 mg
corn starch	34.0 mg
polyvinylpyrrolidone	4.0 mg
magnesium stearate	2.0 mg
	220.0 mg

Method of Preparation:

The active substance, lactose and starch are mixed together and uniformly moistened with an aqueous solution of the polyvinylpyrrolidone. After the moist composition has been screened (2.0 mm mesh size) and dried in a rack-type drier at 50°C it is screened again (1.5 mm mesh size) and the lubricant is added. The finished mixture is compressed to form tablets.

Weight of tablet: 220 mg

Diameter: 10 mm, biplanar, facetted on both sides and notched on one side.

Example 6

Tablets containing 150 mg of active substance

Composition:
1 tablet contains:

active substance	150.0 mg
powdered lactose	89.0 mg
corn starch	40.0 mg
colloidal silica	10.0 mg
polyvinylpyrrolidone	10.0 mg
magnesium stearate	1.0 mg

300.0 mg

Preparation:

The active substance mixed with lactose, corn starch and silica is moistened with a 20% aqueous polyvinylpyrrolidone solution and passed through a screen with a mesh size of 1.5 mm. The granules, dried at 45°C, are passed through the same screen again and mixed with the specified amount of magnesium stearate. Tablets are pressed from the mixture.

Weight of tablet: 300 mg
die: 10 mm, flat

Example 7

Hard gelatine capsules containing 150 mg of active substance

1 capsule contains:

active substance		150.0 mg
corn starch (dried	approx.	180.0 mg
lactose (powdered)	approx.	87.0 mg
magnesium stearate		3.0 mg
	approx.	420.0 mg

Preparation:

The active substance is mixed with the excipients, passed through a screen with a mesh size of 0.75 mm and homogeneously mixed using a suitable apparatus. The finished mixture is packed into size 1 hard gelatine capsules.

Capsule filling: approx. 320 mg
Capsule shell: size 1 hard gelatine capsule.

Example 8

Suppositories containing 150 mg of active substance

1 suppository contains:

active substance	150.0 mg
polyethyleneglycol 1500	550.0 mg
polyethyleneglycol 6000	460.0 mg
polyoxyethylene sorbitan monostearate	840.0 mg
	2,000.0 mg

Preparation:

After the suppository mass has been melted the active substance is homogeneously distributed therein and the melt is poured into chilled moulds.

Example 9

Suspension containing 50 mg of active substance

100 ml of suspension contain:

active substance		1.00 g
carboxymethylcellulose-Na-salt		0.10 g
methyl p-hydroxybenzoate		0.05 g
propyl p-hydroxybenzoate		0.01 g
glucose		10.00 g
glycerol		5.00 g
70% sorbitol solution		20.00 g
flavouring		0.30 g
dist. water	ad	100 ml

Preparation:

The distilled water is heated to 70°C. The methyl and propyl p-hydroxybenzoates together with the glycerol and sodium salt of carboxymethylcellulose are dissolved therein with stirring.

The solution is cooled to ambient temperature and the active substance is added and homogeneously dispersed therein with stirring. After the sugar, the sorbitol solution and the flavouring have been added and dissolved, the suspension is evacuated with stirring to eliminate air.

5 ml of suspension contain 50 mg of active substance.

Example 10

Ampoules containing 10 mg active substance

Composition:

active substance		10.0 mg
0.01 N hydrochloric acid q.s.		
double-distilled water	ad	2.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 2 ml ampoules.

Example 11

Ampoules containing 50 mg of active substance

Composition:

active substance		50.0 mg
0.01 N hydrochloric acid q.s.		
double-distilled water	ad	10.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 10 ml ampoules.

Example 12

Capsules for powder inhalation containing 5 mg of active substance

1 capsule contains:

active substance	5.0 mg
lactose for inhalation	15.0 mg
	20.0 mg

Preparation:
The active substance is mixed with lactose for inhalation. The mixture is packed into capsules in a capsule-making machine (weight of the empty capsule approx. 50 mg).

weight of capsule: 70.0 mg
size of capsule = 3

Example 13

Solution for inhalation for hand-held nebulisers containing 2.5 mg active substance

1 spray contains:

active substance	2.500 mg
benzalkonium chloride	0.001 mg
1N hydrochloric acid q.s.	
ethanol/water (50/50)	ad 15.000 mg

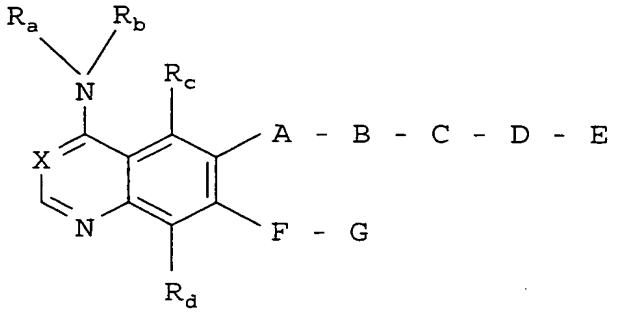
Preparation:
The active substance and benzalkonium chloride are dissolved in ethanol/water (50/50). The pH of the solution is adjusted with 1N hydrochloric acid. The resulting solution is filtered

and transferred into suitable containers for use in hand-held nebulisers (cartridges).

Contents of the container: 4.5 g

Patent Claims

1. Bicyclic heterocycles of general formula



, (I)

wherein

R_a denotes a hydrogen atom or a C_{1-4}-alkyl group,

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_3, whilst

R_1 and R_2, which may be identical or different, in each case denote a hydrogen, fluorine, chlorine, bromine or iodine atom,

a C_{1-4}-alkyl, hydroxy, C_{1-4}-alkoxy, C_{3-6}-cycloalkyl, C_{4-6}-cycloalkoxy, C_{2-5}-alkenyl or C_{2-5}-alkynyl group,

an aryl, aryloxy, arylmethyl or arylmethoxy group,

a C_{3-5}-alkenyloxy or C_{3-5}-alkynyloxy group, wherein the unsaturated moiety may not be linked to the oxygen atom,

a C_{1-4}-alkylsulphenyl, C_{1-4}-alkylsulphinyl, C_{1-4}-alkylsulphonyl, C_{1-4}-alkylsulphonyloxy,

trifluoromethylsulphenyl, trifluoromethylsulphinyl or trifluoromethylsulphonyl group,

a methyl or methoxy group substituted by 1 to 3 fluorine atoms,

an ethyl or ethoxy group substituted by 1 to 5 fluorine atoms,

a cyano or nitro group or an amino group optionally substituted by one or two C_{1-4}-alkyl groups, wherein the substituents may be identical or different, or

R_1 together with R_2, if they are bound to adjacent carbon atoms, denote a -CH=CH-CH=CH, -CH=CH-NH or -CH=N-NH group and

R_3 denotes a hydrogen, fluorine, chlorine or bromine atom,

a C_{1-4}-alkyl, trifluoromethyl or C_{1-4}-alkoxy group,

R_c and R_d, which may be identical or different, in each case denote a hydrogen, fluorine or chlorine atom, a methoxy group, or a methyl group optionally substituted by a methoxy, dimethylamino, diethylamino, pyrrolidino, piperidino or morpholino group,

X denotes a methine group substituted by a cyano group or a nitrogen atom,

A denotes an oxygen atom or an imino group optionally substituted by a C_{1-4}-alkyl group,

B denotes a carbonyl or sulphonyl group,

C denotes a 1,3-allenylene, 1,1- or 1,2-vinylene group which may be substituted in each case by one or two methyl groups or by a trifluoromethyl group,

an ethynylene group or

a 1,3-butadien-1,4-ylene group optionally substituted by 1 to 4 methyl groups or by a trifluoromethyl group,

D denotes an alkylene, -CO-alkylene or -SO_2-alkylene group wherein the alkylene moiety in each case contains 1 to 8 carbon atoms and additionally 1 to 4 hydrogen atoms in the alkylene moiety may be replaced by fluorine atoms, while the linking of the -CO-alkylene or -SO_2-alkylene group to the adjacent group C in each case must take place via the carbonyl or sulphonyl group,

a -CO-O-alkylene, -CO-NR_4-alkylene or -SO_2-NR_4-alkylene group wherein the alkylene moiety in each case contains 1 to 8 carbon atoms, whilst the linking to the adjacent group C in each case must take place via the carbonyl or sulphonyl group, wherein

R_4 denotes a hydrogen atom or a C_{1-4}-alkyl group,

or, if D is bound to a carbon atom of the group E, it may also denote a bond,

or, if D is bound to a nitrogen atom of the group E, it may also denote a carbonyl or sulphonyl group,

E denotes an R_6O-CO-alkylene-NR_5, (R_7O-PO-OR_8)-alkylene-NR_5 or (R_7O-PO-R_9)-alkylene-NR_5-group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C_{1-2}-alkyl groups or by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group, wherein

R_5 denotes a hydrogen atom,

a C_{1-4}-alkyl group, which may be substituted by a hydroxy, C_{1-4}-alkoxy, carboxy, R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), amino, C_{1-4}-alkylamino or di-(C_{1-4}-alkyl)-amino group or by a 4- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, or by a sulphinyl, sulphonyl, imino or N-(C_{1-4}-alkyl)-imino group,

a C_{3-7}-cycloalkyl or C_{3-7}-cycloalkyl-C_{1-3}-alkyl group,

R_6, R_7 and R_8, which may be identical or different, in each case denote a hydrogen atom,

a C_{1-8}-alkyl group, which may be substituted by a hydroxy, C_{1-4}-alkoxy, amino, C_{1-4}-alkylamino or di-(C_{1-4}-alkyl)-amino group or by a 4- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-4}-alkyl)-imino group,

a C_{4-7}-cycloalkyl group optionally substituted by 1 or 2 methyl groups,

a C_{3-5}-alkenyl or C_{3-5}-alkynyl group, wherein the unsaturated moiety may not be linked to the oxygen atom,

a C_{3-7}-cycloalkyl-C_{1-4}-alkyl, aryl, aryl-C_{1-4}-alkyl or R_9CO-O-(R_eCR_f)-group, whilst

R_e and R_f, which may be identical or different, in each case denote a hydrogen atom or a C_{1-4}-alkyl group and

R_9 denotes a C_{1-4}-alkyl, C_{3-7}-cycloalkyl, C_{1-4}-alkoxy or C_{5-7}-cycloalkoxy group,

and R_9 denotes a C_{1-4}-alkyl, aryl or aryl-C_{1-4}-alkyl group,

a 4- to 7-membered alkyleneimino group which may be substituted by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and is additionally substituted at a cyclic carbon atom by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined and

R_{10} denotes a hydrogen atom, a C_{1-4}-alkyl, formyl, C_{1-4}-alkylcarbonyl or C_{1-4}-alkylsulphonyl group,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10} while the abovementioned 5- to 7-membered rings are additionally substituted in each case at a carbon atom by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_{10} are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl,

bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group, wherein R_6 to R_9 are as hereinbefore defined,

a 2-oxo-morpholino group which may be substituted by 1 or 2 methyl groups,

an amino group or an amino group optionally substituted by 1 or 2 C_{1-4}-alkyl groups wherein the alkyl groups may be identical or different and each alkyl moiety may be substituted from position 2 by a hydroxy, C_{1-4}-alkoxy, amino, C_{1-4}-alkylamino or di-(C_{1-4}-alkyl)-amino group or by a 4- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group may be replaced in the 4 position by an oxygen or sulphur atom, or by a sulphinyl, sulphonyl, imino or N-(C_{1-4}-alkyl)-imino group,

an 4- to 7-membered alkyleneimino group optionally substituted by 1 to 4 methyl groups,

a 6- to 7-membered alkyleneimino group optionally substituted by 1 or 2 methyl groups wherein in each case a methylene group in the 4 position is replaced by an oxygen or sulphur atom, by an imino group substituted by the group R_{10}, or by a sulphinyl or sulphonyl group, wherein R_{10} is as hereinbefore defined,

an imidazolyl group optionally substituted by 1 to 3 methyl groups,

a C_{5-7}-cycloalkyl group wherein a methylene group is replaced by an oxygen or sulphur atom, by an imino group substituted by the group R_{10}, by a sulphinyl or sulphonyl group, wherein R_{10} is as hereinbefore defined,

or D together with E denotes a hydrogen, fluorine or chlorine atom,

a C_{1-4}-alkyl group optionally substituted by 1 to 5 fluorine atoms,

a C_{3-6}-cycloalkyl group,

an aryl, heteroaryl, C_{1-4}-alkylcarbonyl, arylcarbonyl, carboxy, C_{1-4}-alkoxycarbonyl, $R_gCO-O-(R_eCR_f)-O-CO$, $(R_7O-PO-OR_8)$ or $(R_7O-PO-R_9)$-group wherein R_e to R_g and R_7 to R_9 are as hereinbefore defined,

an aminocarbonyl, C_{1-4}-alkylaminocarbonyl or di-$(C_{1-4}$-alkyl)-aminocarbonyl group or

a carbonyl group, which is substituted by a 4- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by an imino group substituted by the group R_{10}, by a sulphinyl or sulphonyl group, while R_{10} is as hereinbefore defined,

F denotes a C_{1-6}-alkylene group, an $-O-C_{1-6}$-alkylene group, whilst the alkylene moiety is linked to the group G, or an oxygen atom, whilst the latter may not be linked to a nitrogen atom of the group G, and

G denotes an R_6O-CO-alkylene-NR_5, $(R_7O-PO-OR_8)$-alkylene-NR_5 or $(R_7O-PO-R_9)$-alkylene-NR_5-group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C_{1-2}-alkyl groups or by an R_6O-CO or $R_6O-CO-C_{1-2}$-alkyl group, wherein R_5 to R_9 are as hereinbefore defined,

a 4- to 7-membered alkyleneimino group which is substituted by an R_6O-CO, $(R_7O-PO-OR_8)$, $(R_7O-PO-R_9)$, $R_6O-CO-C_{1-4}$-alkyl, bis-$(R_6O-CO)-C_{1-4}$-alkyl, $(R_7O-PO-OR_8)-C_{1-4}$-alkyl or $(R_7O-PO-R_9)-C_{1-4}$-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and is additionally substituted at a cyclic carbon atom by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_{10} are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10}, whilst the abovementioned 5- to 7-membered rings are additionally substituted in each case at a carbon atom by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-pO-OR_8)-C_{1-4}-alkyl or (R_7O-pO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_{10} are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group, wherein R_6 to R_9 are as hereinbefore defined,

a 2-oxo-morpholino group which may be substituted by 1 or 2 methyl groups,

a 2-oxo-morpholinyl group which is substituted in the 4 position by a hydrogen atom, by a C_{1-4}-alkyl, R_6O-CO-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group, while R_6 to R_9 are as hereinbefore defined and the abovementioned 2-oxo-morpholinyl groups are linked in each case to a carbon atom of the group F,

an amino group or an amino group optionally substituted by 1 or 2 C_{1-4}-alkyl groups wherein the alkyl groups may be identical or different and each alkyl moiety may be substituted from position 2 by a hydroxy, C_{1-4}-alkoxy, amino, C_{1-4}-alkylamino or di-(C_{1-4}-alkyl)-amino group or by a 4- to 7-membered alkyleneimino group, wherein in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-4}-alkyl)-imino group,

a 4- to 7-membered alkyleneimino group optionally substituted by 1 to 4 methyl groups,

a 6- to 7-membered alkyleneimino group optionally substituted by 1 or 2 methyl groups wherein in each case a methylene group in the 4 position is replaced by an oxygen or sulphur atom, by an imino group substituted by the group R_{10}, or by a sulphinyl or sulphonyl group, wherein R_{10} is as hereinbefore defined,

an imidazolyl group optionally substituted by 1 to 3 methyl groups,

a C_{5-7}-cycloalkyl group wherein a methylene group is replaced by an oxygen or sulphur atom, by an imino group substituted by the group R_{10}, or by a sulphinyl or sulphonyl group, wherein R_{10} is as hereinbefore defined, or

F and G together denote a hydrogen, fluorine or chlorine atom,

a C_{1-6}-alkoxy group optionally substituted from position 2 by a hydroxy or C_{1-4}-alkoxy group,

a C_{1-6}-alkoxy group which is substituted by an R_6O-CO, (R_7O-PO-OR_8) or (R_7O-PO-R_9)-group, while R_6 to R_9 are as hereinbefore defined,

a C_{4-7}-cycloalkoxy or C_{3-7}-cycloalkyl-C_{1-4}-alkoxy group, an amino group optionally substituted by 1 or 2 C_{1-4}-alkyl groups,

a 5- to 7-membered alkyleneimino group, wherein in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by an imino group substituted by the group R_{10}, or by a sulphinyl or sulphonyl group, while R_{10} is as hereinbefore defined,

with the proviso that at least one of the groups E, G or F together with G denotes a R_6O-CO, (R_7O-PO-OR_8) or (R_7O-PO-R_9)-group or

D together with E contains an R_gCO-O-(R_eCR_f)-O-CO, (R_7O-PO-OR_8) or (R_7O-PO-R_9)-group or

E or G contains an optionally substituted 2-oxo-morpholinyl group,

whilst by the aryl moieties mentioned in the definitions of the abovementioned groups is meant a phenyl group which may in each case be monosubstituted by R_{12}, mono-, di- or trisubstituted by R_{13} or monosubstituted by R_{12} and additionally mono- or disubstituted by R_{13}, wherein the substituents may be identical or different and

R_{12} denotes a cyano, carboxy, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-4}-alkylaminocarbonyl, di-(C_{1-4}-alkyl)-aminocarbonyl, C_{1-4}-alkylsulphenyl, C_{1-4}-alkylsulphinyl, C_{1-4}-alkylsulphonyl, hydroxy, C_{1-4}-alkylsulphonyloxy, trifluoromethyloxy, nitro, amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, C_{1-4}-alkylcarbonylamino, N-(C_{1-4}-alkyl)-C_{1-4}-alkylcarbonylamino, C_{1-4}-alkylsulphonylamino, N-(C_{1-4}-alkyl)-C_{1-4}-alkylsulphonylamino, aminosulphonyl, C_{1-4}-alkylaminosulphonyl or di-(C_{1-4}-alkyl)-aminosulphonyl group or a carbonyl group, which is substituted by a 5- to 7-membered alkyleneimino group,

while in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-4}-alkyl)-imino-group, and

R_{13} denotes a fluorine, chlorine, bromine or iodine atom, a C_{1-4}-alkyl, trifluoromethyl or C_{1-4}-alkoxy group or

two groups R_{13}, if they are bound to adjacent carbon atoms, together denote a C_{3-5}-alkylene, methylenedioxy or 1,3-butadien-1,4-ylene group,

and moreover by the heteroaryl groups mentioned in the definitions of the abovementioned groups is meant a 5-membered heteroaromatic group which contains an imino group, an oxygen or sulphur atom or an imino group, an oxygen or sulphur atom and one or two nitrogen atoms, or

a 6-membered heteroaromatic group, which contains one, two or three nitrogen atoms,

whilst the abovementioned 5-membered heteroaromatic groups may be substituted in each case by 1 or 2 methyl or ethyl groups and the abovementioned 6-membered heteroaromatic groups may be substituted in each case by 1 or 2 methyl or ethyl groups or by a fluorine, chlorine, bromine or iodine atom, or by a trifluoromethyl, hydroxy, methoxy or ethoxy group,

the tautomers, the stereoisomers and the salts thereof.

2. Bicyclic heterocycles of general formula I according to claim 1, wherein

R_a denotes a hydrogen atom,

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_3, wherein

R_1 and R_2, which may be identical or different, in each case denote a hydrogen, fluorine, chlorine or bromine atom,

a methyl, trifluoromethyl, ethynyl, methoxy or cyano group and

R_3 denotes a hydrogen atom,

R_c and R_d in each case denote a hydrogen atom,

X denotes a methine group substituted by a cyano group or a nitrogen atom,

A denotes an imino group,

B denotes a carbonyl group,

C denotes a 1,1- or 1,2-vinylene group, an ethynylene or 1,3-butadien-1,4-ylene group,

D denotes a straight-chained C_{1-3}-alkylene group or a -CO-NH-C_{2-3}-alkylene group wherein the alkylene moiety is a straight chain and the linking to the adjacent group C takes place via the carbonyl group,

or, if D is bound to a carbon atom of the group E, it may also denote a bond,

E denotes an R_6O-CO-alkylene-NR_5-group wherein the alkylene moiety, which is straight-chained and contains 1 to 3 carbon atoms, may additionally be substituted by a methyl, methoxycarbonyl, ethoxycarbonyl, methoxycarbonylmethyl or ethoxycarbonylmethyl group, wherein

R_5 denotes a C_{1-4}-alkyl, R_6O-CO-CH_2, cyclopropyl or cyclopropylmethyl group and

R_6 denotes a C_{1-6}-alkyl, cyclopentyl, cyclohexyl, C_{3-6}-cycloalkylmethyl or benzyl group,

a pyrrolidino or piperidino group substituted by an R_6O-CO group or a piperidino group substituted by an R_6O-CO-CH_2 group wherein R_6 is as hereinbefore defined,

a 4-piperidinyl group, which is substituted in the 1 position by an R_6O-CO-C_{1-3}-alkyl group wherein the alkyl moiety is straight-chained and R_6 is as hereinbefore defined,

a piperazino group which is substituted in the 4 position by an R_6O-CO-C_{1-3}-alkyl group wherein the alkyl moiety is straight-chained and R_6 is as hereinbefore defined,

a piperazino group which is substituted in the 4 position by a methyl group and in the 2 or 3 position by an R_6O-CO- group, while R_6 is as hereinbefore defined,

an (R_7O-PO-OR_8)-CH_2-NR_5 or (R_7O-PO-R_9)-CH_2-NR_5-group, while R_5 is as hereinbefore defined,

R_7 and R_8, which may be identical or different, in each case denote a methyl, ethyl or R_gCO-O-(R_eCR_f) group, wherein

R_e denotes a hydrogen atom or a C_{1-4}-alkyl group,

R_f denotes a hydrogen atom and

R_g denotes a C_{1-4}-alkyl, C_{1-4}-alkoxy or C_{5-6}-cycloalkoxy group,

and R_9 denotes a methyl or ethyl group,

or D together with E denotes a hydrogen atom, a methyl, trifluoromethyl, phenyl or R_gCO-O-(R_eCR_f)-O-CO group wherein R_e to R_g are as hereinbefore defined,

F denotes an -O-C_{1-4}-alkylene group wherein the alkylene moiety, which is preferably straight-chained, is linked to the group G, or an oxygen atom, although this may not be linked to a nitrogen atom of the group G, and

G denotes an R_6O-CO-alkylene-NR_5-group wherein the alkylene moiety, which is straight-chained and contains 1 to 3 carbon atoms, may additionally be substituted by a methyl, methoxycarbonyl, ethoxycarbonyl, methoxycarbonylmethyl or ethoxycarbonylmethyl group, wherein R_5 and R_6 are as hereinbefore defined,

a pyrrolidino or piperidino group substituted by an R_6O-CO-group or a piperidino group substituted by an R_6O-CO-CH_2-group wherein R_6 is as hereinbefore defined,

a 4-piperidinyl group, which is substituted in the 1 position by an R_6O-CO-C_{1-3}-alkyl group, wherein the alkyl moiety is a straight chain and R_6 is as hereinbefore defined,

a piperazino group which is substituted in the 4 position by an R_6O-CO-C_{1-3}-alkyl group, wherein the alkyl moiety is straight-chained and R_6 is as hereinbefore defined,

or F and G together denote a hydrogen atom or a C_{1-3}-alkoxy group optionally substituted by an R_6O-CO-group wherein R_6 is as hereinbefore defined,

with the proviso that at least one of the groups E, G or F together with G contains an R_6O-CO, (R_7O-PO-OR_8) or (R_7O-PO-CH_3) group or

D together with E contains an $R_gCO-O-(R_eCR_f)-O-CO$ group,

the tautomers, the stereoisomers and the salts thereof.

3. Bicyclic heterocycles of general formula I according to claim 1, wherein

R_a denotes a hydrogen atom,

R_b denotes a phenyl group substituted by the groups R_1 to R_3 wherein

R_1 and R_2, which may be identical or different, in each case denote a hydrogen, fluorine, chlorine or bromine atom and

R_3 denotes a hydrogen atom,

R_c and R_d in each case denote a hydrogen atom,

X denotes a nitrogen atom,

A denotes an imino group,

B denotes a carbonyl group,

C denotes a 1,2-vinylene group,

D denotes a methylene or $-CO-NH-C_{2-3}$-alkylene group wherein the alkylene moiety is a straight chain and the linking to the adjacent group C takes place via the carbonyl group,

E denotes an $R_6O-CO-CH_2-NR_5-$ group wherein

R_5 denotes a methyl or $R_6O-CO-CH_2$ group and R_6 in each case denotes a C_{1-4}-alkyl or cyclohexyl group,

or D together with E denotes a hydrogen atom or a methyl group,

F denotes a -O-C_{1-3}-alkylene group wherein the alkylene moiety is straight-chained and is linked to the group G, or an oxygen atom, although this may not be linked to a nitrogen atom of the group G, and

G denotes a 4-piperidinyl group which is substituted in the 1 position by an R_6O-CO-C_{1-3}-alkyl group, or a piperazino group which is substituted in the 4 position by an R_6O-CO-C_{1-3}-alkyl group wherein in each case the alkyl moiety is straight-chained and R_6 is as hereinbefore defined,

or F and G together denote a hydrogen atom or a methoxy group with the proviso that at least one of the groups E or G contains an R_6O-CO group,

the tautomers, the stereoisomers and the salts thereof.

4. Physiologically acceptable salts of the compounds according to at least one of claims 1 to 3 with inorganic or organic acids or bases.

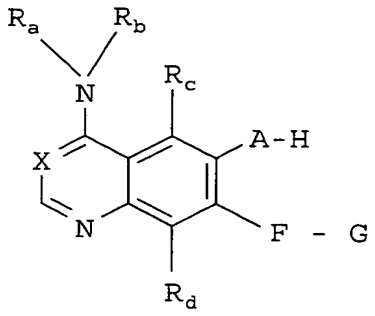
5. Pharmaceutical compositions containing a compound according to at least one of claims 1 to 3 or a physiologically acceptable salt according to claim 4 optionally together with one or more inert carriers and/or diluents.

6. Use of a compound according to at least one of claims 1 to 4 for preparing a pharmaceutical composition which is suitable for treating benign or malignant tumours, for preventing and treating diseases of the airways and lungs and for treating diseases of the gastrointestinal tract and the bile duct and gall bladder.

7. Process for preparing a pharmaceutical composition according to claim 5, characterised in that a compound according to at least one of claims 1 to 4 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

8. Process for preparing the compounds of general formula I according to claims 1 to 4, characterised in that

a) a compound of general formula



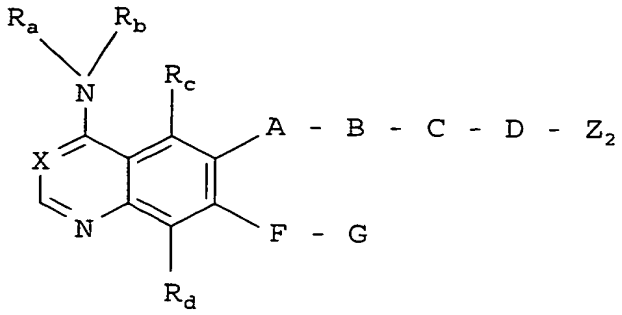
, (II)

wherein
R_a to R_d, A, F, G and X are defined as in claims 1 to 3, is reacted with a compound of general formula

$$Z_1 - B - C - D - E \qquad , (III)$$

wherein
B to E are defined as in claims 1 to 3 and
Z_1 denotes a leaving group or a hydroxy group, or

b) in order to prepare compounds of general formula I wherein the group E is linked to the group D via a nitrogen atom, a compound of general formula



, (IV)

wherein
R_a to R_d, A to D, F, G and X are defined as in claims 1 to 3 and
Z_2 denotes a leaving group, is reacted with a compound of general formula

H - E´ , (V)

wherein
E´ denotes one of the groups mentioned for E in claims 1 to 3, which is linked to the group D via a nitrogen atom, and

if desired a compound of general formula I thus obtained which contains an amino, alkylamino or imino group is converted by acylation or sulphonylation into a corresponding acyl or sulphonyl compound of general formula I and/or

a compound of general formula I thus obtained which contains an amino, alkylamino or imino group, is converted by alkylation or reductive alkylation into a corresponding alkyl compound of general formula I and/or

a compound of general formula I thus obtained which contains a carboxy or hydroxyphosphoryl group is converted by esterification into a corresponding ester of general formula I and/or

a compound of general formula I thus obtained which contains a carboxy or ester group is converted by reaction with a corresponding amine into a corresponding amide of general formula I and/or

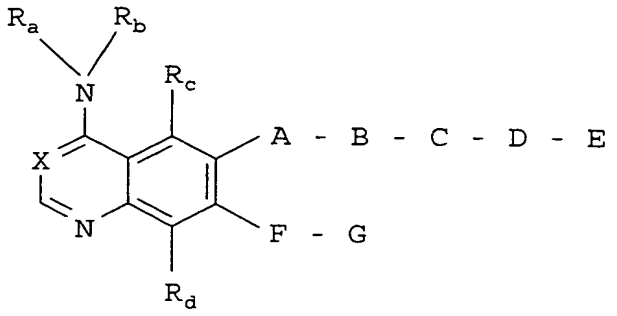
if necessary any protecting group used during the reactions described above is cleaved again and/or

if desired a compound of general formula I thus obtained is resolved into the stereoisomers thereof and/or

a compound of general formula I thus obtained is converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts thereof.

Abstract

The present invention relates to bicyclic heterocycles of general formula



, (I)

wherein

R_a to R_d, A to G and X are defined as in claim 1, the tautomers, the stereoisomers and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases which have valuable pharmacological properties, particularly an inhibiting effect on signal transduction mediated by tyrosine kinases, their use for treating diseases, particularly tumoral diseases, diseases of the lungs and respiratory text and the preparation thereof.